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ANXIETY: DAMAGE AND REPAIR*

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ANXIETY is one of the most common conditions with which the physician has to deal. And yet, until recently, relatively little has been understood either about its manifestations or about its management. The detailed reasons for this need not concern us in this presentation; it is sufficient to say that they have nothing to do with the complexity of the matter, but are to be found rather in certain attitudes among the laity and medical men alike. Chief among these is, first, the traditional idea of a separation between the mind and the body; second, social deprecation of anxiety; and third, the exceedingly commonly used method of controlling anxiety by attempting to put it out of one's mind, *i.e.*, by suppression and repression.

It has been an essential preliminary task to attempt to break up these prevalent premises. Some degree of success has been obtained, and we are now engaged in bringing our techniques and working hypotheses concerning anxiety to a level of equal development with the general conceptual framework of the rest of medical science.

This paper deals with certain aspects of this endeavour. There is a triad of assumptions concerning anxiety which is now generally accepted. This is (1) that the capacity to develop anxiety is inborn, but the cues which will evoke anxiety are mainly or entirely learned; (2) that anxiety is normal; and (3) that anxiety is a total reaction, involving not simply the feeling of anxiety but also changes at the physiological, biochemical and (if long continued) the structural levels.

This third premise is under particularly active exploration in the present decade, and, to use an archæological term, it has been the major dig of the psychosomatic research worker, from which he has brought up such ancient facts, long hidden from our sight by cultural misconceptions, as that chronic anxiety will produce not only loss of weight but occasionally quite excessive obesity, that it causes severe exhaustion, that it plays an exceedingly important part in ulcer formation in the gastro-intestinal tract, and that it is a factor in many dermatological conditions.

At the Allan Memorial Institute, we have been concerned with several aspects of this damage caused by intense or chronic anxiety. This paper deals with a particular segment, namely, with the damage which may be sustained by the anxiety mechanisms themselves.

To illustrate this by analogy, let us say that we recognize that the heat control mechanism, consisting as it does of certain neural centres, of activities of the skin and lungs, the constriction and dilatation of vessels, may itself break down and lead to pathological functioning, and that this is quite apart from the damage which the organism may suffer from exposure to severe cold or heat in the presence of an intact, but temporarily overborne, heat control mechanism.

So it is with the mechanism of anxiety. And we are concerned with the damage which that mechanism may suffer and with how it is repaired.

In considering this, let us look at certain functions within the mechanism of anxiety. First of all, there is the function of generalization. From clinical observation and from the work of experimental psychologists we have derived some knowledge of the process of generalization of the cue, and are now inquiring into what has been termed generalization of the response.

By generalization of the cue is meant that where a particularly powerful anxiety has been elicited by a given cue or situation, there then is set up a tendency for the individual to react again by anxiety not simply to that specific cue but also to all similar cues or situations.

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Translating this into everyday terms, we see generalization taking place where the little girl is threatened by a rough and forceful examination of her tonsils and adenoids. She is now afraid of her doctor and this fear spreads to all doctors, to certain symbols of medicine such as the doctor's office, the odor of disinfectants and the presence of the uniformed nurse. Or, take for illustration the case of a recent patient.

Here, as you will see, the anxiety was first set up not entirely upon the basis of the reality situation, namely, the situation as you and I might have seen it had we been present at the time, but largely upon the basis of the unconscious meaning to the patient of the event. This event was a discussion which he was carrying on with a friend as they were riding in a streetcar. The friend was telling him about an operation which he had had upon his nose, and the patient began inexplicably to grow so anxious that he fainted. It was only fourteen years later, when he was under psychotherapy, that it was possible to bring out the fact that his intense anxiety on hearing of this operation arose from his profound sexual conflicts and particularly from the struggles which he was then having with his grim and depriving father.

The immediate results of this intense anxiety reaction were a generalization of his fears. All discussions about nose operations became anxiety producing. Then he became fearful of hearing about any surgical procedures, and his anxiety spread to doctors in general and to all medical activities. Finally, it spread to the whole matter of talking to people. This latter development of the generalization of his anxiety can only be understood when it is realized that the patient sees his talking as an aggressive activity, and indeed it is interesting to note with what vehemence this able young businessman throws himself into any discussion. He feels that he is hitting out at people with his phrases and his gestures.

Now this spread of his anxiety to his own aggressiveness can be understood when we refer back to his struggles with his father, his hostility to him and his guilty fears over his antagonism, and once again to the fears of his father's counter-hostility and possible punitive attitudes. The fears had come to a point of great intensity in connection with discussion of the nose operation which symbolized the patient's sex conflicts and his fears of his father's punishment therefor.

These two cases provide illustrations of how extensive generalization may become. The one case follows a relatively simple design, all the components of which are open to our immediate inspection. The other case is much more complex, but mainly so because most of the more important interconnections are repressed and hence can be brought out and understood by the physician and the patient alike only after detailed exploration.

The matter of fundamental importance which these illustrations are meant to illuminate is that where generalization takes place, the anxiety system will go into anticipatory activity on the basis of a considerable range of situations which actually constitute no threat whatsoever to the individual. In other words, the anxiety system has developed a defect which can quite severely reduce the effectiveness of the individual.

What do we know of the circumstances under which generalization takes place? We may say first that it bears a positive relationship to the intensity of the response. Where, for instance, the individual is intensely frightened in a given situation, there is an increased probability that generalization will be extensive. A second set of facts is also known, namely, that the more similar the situations or cues, the more probable it is that they will be subject to generalization. The term "gradient of generalization" has been used to express this.

Finally, we may put forward certain suggestions, as yet unverified, as to the period during which generalization is particularly apt to occur. Tyhurst (1951), in studies undertaken at this Institute upon civilian disasters, found it useful to categorize the behaviour of the individual exposed to disaster in three phases: that of impact—the actual exposure to the stress of the fire and the explosion; the period of recoil; and the post-traumatic period. It would seem probable that it is during the third period, when full awareness of the extent and meaning of the disaster has been established, that the process of generalization takes place.

Certainly it can be said from other studies—such as the Cocoanut Grove fire (Adler, 1943)—that those individuals who became unconscious early in the disaster and remained unconscious for at least an hour appeared to have suffered fewer lasting effects than those who remained conscious throughout.

As will readily be understood, further studies of disasters are likely to afford us most valuable leads as to when and how not only excessive

generalization but other forms of damage by anxiety take place.

Generalization may be seen as something of a massive and perhaps elementary attempt at self-protection. It results in all, or nearly all, the circumstances in a dangerous situation becoming cues to set up the anxiety response in the future. Differentiation, in contrast, is the process whereby we learn to respond more and more selectively to situations. These two are somewhat in opposition, for whenever the intensity of the reaction to a situation rises, differentiation tends to break down. Generalization is thus in some respects a retreat into mass action, while differentiation is the road to the development of new, more highly discriminatory behaviour.

We have explored this concept of generalization of the cue and have indicated that wherever it occurs to excessive degree, it must be seen as decreasing the effectiveness of the individual; in a word, as evidence of damage having been sustained by the anxiety system.

Earlier we had referred to generalization of the response. By this is meant that not only may the events under which the anxiety is experienced become cues for its subsequent elicitation, as we have just observed, but the patient's mood and general set which was in existence at the time that the individual was exposed to the anxiety producing situation may become so bound up with the anxiety response that a strong tendency is established for both to occur simultaneously from that point on.

Time will have to verify or disprove the usefulness of this conception, but at least one may say that no matter how we may eventually decide to conceptualize them, the facts are already well recognized, for we know that many moods and emotional responses, even the most contradictory, may come to serve as cues for the elicitation of anxiety.

Let us take first one interconnection which is well known, namely, that between anxiety and the sexual response. So many are the prohibitions in our society to the free expression of the sexual response that in almost everyone it becomes, at least to some degree, cross-connected to anxiety. In other words, it is exceedingly rare to find anyone in whom sexual activity is not either habitually or frequently carried out with some anxiety.

In some individuals, this generalization of anxiety to the sexual response is most extensive. This is well shown in a young girl who had carried on sexual relations from about the age of six, against extreme prohibitions on the part of her mother. The mother and the girl were engaged in a bitter struggle for dominance; the girl's sexuality became one of their battlegrounds, the mother attempting to eliminate it entirely, the patient insisting with great guilt and anxiety in asserting her right to independence.

When she was first seen, after ten years of this struggle, she was entirely unable to differentiate between anxiety and sexuality. The slightest premonitory rise in sex interest—for instance, on meeting a boy or getting ready to go to a dance—was perceived as anxiety, and such typical anxiety feelings as "butterflies in the stomach" were thought of as a sexual response. In both those situations which would be construed by an outsider as likely to evoke sexual interest or those likely to produce anxiety, there would result, in inextricable medley, sexual and anxiety responses: there would be an increased vaginal secretion and at the time her hands would become blue and cold, her nipples would become erect and at the same time she would describe herself as feeling scared.

While such far-reaching generalizations are less common, it is a matter of more frequent experience to encounter the individual in whom the sexual response can take form and proceed normally for varying distances, but after a certain point has been reached anxiety is cued into existence, which may result in inhibiting the sexual response. This is true of many failures to maintain an erection in men and it is also true of a certain number of cases of vaginismus.

This cross-connecting and generalizing of response has been illustrated in the sexual field because of its frequency, but it would appear probable that it takes place in association with any of the strong intensifications of behaviour—anger, shame, guilt, depression. We see many instances where one's own anger arouses anxiety in oneself, and where, conversely, one grows angry in the course of being afraid.

From these remarks concerning the generalization of response, it will be seen that just as in the case of the generalization of the cue, this may become so extensive and result in such contradictions and conflicts in behaviour as to constitute once more a serious defect, a defect which finds its origin in this essential aspect of the anxiety system.

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Repair is presently achieved mainly by reversal of the two factors which promote generalization, namely, intensity of the anxiety and similarity of the cues. Modern psychotherapeutic methods include many procedures such as, desensitization and deconditioning, which achieve the first; and reassessment techniques are used to promote the breakup of similarity.

Let us turn now to an entirely different kind of damage. Everybody no matter what his field or practice is familiar with the woman who is fearful about many things. She fidgets if the children are not at home by four o'clock, and her fidgets grow by leaps and bounds to unceasing apprehension as the hours slip by. Every pain and minor complaint serves to spark the near certainty of cancer and coronary disease; she cannot stand crowds, cannot travel on buses; she sleeps poorly, her appetite is spotty, she can't relax, and has a great range of tensional symptoms—pains at the back of her neck, headaches, tremor, fast pulse, exaggerated tendon reflexes among others. To her many fears are added perpetual worry over the fact that she can't concentrate as well as she used to, that her memory is not so reliable, and that she simply can't make decisions.

Our rapidly expanding fund of knowledge concerning the chronic anxiety states now contains many observations and reports which show that this common syndrome is by no means confined to women but is to be encountered wherever men or women have been exposed to too much stress for too long.

Hence we find just such a constellation of complaints in men who have been left in combat too long (Swank), or in men and women who have been held on certain kinds of industrial jobs—particularly highspeed, repetitious work—for periods beyond their tolerance. Recently, attempts have been made to work out a comprehensive term which would cover these various noxious situations, and Liddell (1950), on the basis of his work upon the experimental neurosis in animals, has come forward with the concept of vigilance. He suggests that where the individual maintains, over an excessively prolonged period, an attitude of expectancy or keyed-up preparation for action, anxiety is apt to supervene. Such an attitude is seen as an intensification of the Pavlovian orientation reflex – his "What is it?" response.

This new concept has a special virtue insofar that it permits the inclusion of situations which are not in themselves perceived as a threat by the individual, and which, nonetheless, do result in an elicitation of the anxiety response, for observation is in direct contradiction to the stereotypes of anxiety which are usually held by the laity, *i.e.*, that you are anxious because something threatens you.

But we have come to see that anxiety responses may appear in individuals who, for instance, operate machines which turn out, by separate operations, 18,000 paper bags a day, or who have to sort out some 12,000 screws per shift, placing the damaged ones in a container on the left and the acceptable ones in a tray on the right. We have also reports (Wortis, 1950) of anxiety states appearing in individuals who have been assigned to monotonous sentry duty which involved their patrolling, month after month, a pier where no threat, or indeed any other happening, ever took place, but which, nonetheless, had to be guarded with vigilance.

Whatever the stress, whether it is perceived as threat or whether it takes the form of vigilance, if it is maintained for an excessive period of time it will result in damage. That damage is not limited to the fact that it produces harassing anxiety. By far the more important point is that the anxiety response tends to become self-perpetuating.

Our understanding of this has been delayed by the very extent to which we have attempted to discipline our thinking to the scientific methodology of an earlier period. For, basic to a great deal of 19th century scientific work has been a belief in a deterministic causality. This runs: A causes B, B causes C; stop A and you will stop B and this will stop C. This has worked well enough for many events in physics and chemistry. It ceases to be entirely reliable whenever we begin to deal with living material, and becomes increasingly unreliable the more complex the level of human activity at which we work. The reason for this is that living things are adaptive, and by the very fact of their reaction they alter their reactivity.

How can we account for the perpetuation of these chronic anxiety states? We can do so by postulating a second kind of causal relationship—a circular or autonomous linkage, whereby A causes B, B causes C and C causes A. And this appears to fit in very well with the facts which we possess concerning the autonomous anxiety states. For we can show that, in such states, the reactivity of the anxiety system has

increased by the very fact that it has been excessively called upon (Cameron, 1944). It has been increased to the point that the minor stresses of the day are now sufficient to call it into action, and by calling it into action serve to maintain its increased level of reactivity.

There is available a great range of experimental studies which serve to demonstrate that we are in continual reaction to various stresses imposed by our environment which are not necessarily perceived as such. It can be shown, for instance, that the entry of a new person into the room, the asking of an everyday question, the taking of the pulse and blood pressure, and, indeed, anything which causes us to pay attention is of necessity accompanied by a shift in tensional level, no matter how slight. These shifts can be picked up in the pulse rate, in the skin resistance, in respiratory curves and in the electromyogram.

It can equally readily be shown that in the case of the patient suffering from a chronic anxiety neurosis, the response to these minor stresses is far greater, and, indeed, where the stress stimulus is somewhat greater—such as is constituted by the injection of adrenalin or mecholyl—quite a serious anxiety response may be elicited (Lindemann). This increased reactivity of the anxiety system is to be considered the basis of many of the harassing limitations of which the anxiety neurotic patient complains. He is not able to meet strangers, he is not able to stay in any place which requires a prolonged formalization of his behaviour, *e.g.*, at weddings, nor can he stay for long in the milling crowds of the shopping areas or drive in heavy traffic. All this is because the tensional rises, inseparable from such happenings and endured with little awareness by most people, serve to trigger off his much more highly reactive anxiety system.

Turning now to the matter of the repair of this form of damage to the anxiety system, let us say first that it is our experience that where this damage has become extensive and has lasted for more than three or four years, spontaneous recovery is rare.

The autonomous anxiety state is self-perpetuating. In the earlier and less severe cases where recovery does take place, repair seems to be based upon the following principles: (a) the less frequently a reaction comes into activity, the less likely it is to persist; (b) the reducing of the general tensional level serves to eliminate the probabilities of the appearance of the anxiety response.

It may be said that, fortunately, many of the symptoms of the chronically anxious person facilitate the application of these principles, for his growing difficulties in concentration and in remembering and his fatigue lead sooner or later to a withdrawal from stress producing work, or render him so ineffective that he cannot carry on with dangerous military missions. Moreover, the very nature of the feeling of anxiety is such as to cause the individual to retreat. Here, of course, one must point to the highly motivated, overconscientious people whose very ideals prevent them from doing so, and who for this reason are likely to be the greater sufferers from such conditions.

But where, as in the case of the overmotivated individual, or where for other reasons there was no possibility of escape from stress, the condition becomes firmly established and self-sustaining, repair may still be possible, but now only with outside assistance. In general, that assistance is set up to operate on the basis of the principles mentioned above. Insulin is used for its damping properties, as are sedatives; psychotherapy of a supportive nature, and physiotherapy, are used to lower the general tensional level and thus reduce the probability of further elicitation of refreshment of the anxiety response.

We have described two forms of damage to which the anxiety system is liable—excessive generalization and the development of autonomous states. Other forms of damage are presently being explored and described. We may point to those instances where there is an imbalance in participation of the various aspects of the organism in his anxiety reaction. There are individuals who show a most extensive traumatic response, who are quite frustrated by anxiety, feel fatigued and weak, feel as though they had been beaten all over, and show excessive participation by their cardiovascular, gastro-intestinal and other systems. There are others in whom one particular area becomes the prime field of expression and who habitually respond to anxiety by congestion of the lining of their sinuses, or by gastric participation leading to ulcer formation.

We are beginning to study damage which expresses itself in failure of the curbs which we have developed to limit the exhausting and damaging effects of long-continued anxiety. Such curbs are our mechanisms for suppression and repression, our mechanism for getting re-

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assurance with respect to an uncontrollable situation by setting up and successfully operating a minor one, such as, not stepping on the cracks in the pavement. There are many others of our curbs which may suffer damage and may in themselves come to constitute problems and disturbances to our effective functioning.

BIBLIOGRAPHY

1. ADLER, A.: *J. A. M. A.*, **123**: 1098, 1943.
2. CAMERON, D. E.: *Psychanalyst. Quar.*, **18**: 53, 1944.
3. LIDDELL, H. S.: The Rôle of Vigilance in the Development of Animal Neurosis, Anxiety, Grune & Stratton, N.Y., p. 183, 1950.
4. LINDEMANN, E. AND FINESINGER, J. E.: *Am. J. Psychiat.*, **95**: 353, 1938.
5. SWANK, R. L.: *Arch. Neurol. & Psychiat.*, **55**: 236, 1946.
6. TYHURST, J. S.: *Am. J. Psychiat.*, **107**: 764, 1951.
7. WORTIS, J.: Discussion of Physiological Approach, Anxiety, Grune & Stratton, N.Y., p. 243, 1950.

THE VALUE OF AUREOMYCIN IN PREVENTION OF CROSS INFECTION IN THE HOSPITAL FOR SICK CHILDREN*

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DURING THE SUMMER of 1949 there was a small epidemic of acute nutritional disturbance in this Hospital, characterized by diarrhœa, vomiting, dehydration and toxæmia in infants. This was extremely severe, not improving with the usual type of therapy and in spite of methods for the treatment of dehydration, it continued. Finally, it was found that aureomycin was effective in controlling this infection. There was considerable cross infection and finally it hit our premature unit. With the employing of aureomycin, it was soon eliminated. Because of the success of this, as a prophylactic measure, we placed all† of the premature babies in our unit on aureomycin, 50 mgm. daily, since that time. It is given in the form of spersoids, 2 tsp. daily, twelve hours apart.

In this paper we have taken a group of premature babies who were admitted between August, 1949 and February 4, 1951 (when the hospital was moved from the old building), and a similar group for comparison who were admitted between August, 1947 and February, 1949. The group from August, 1949 to February, 1951 received aureomycin, the previous group did not. The two groups of premature babies were compared to see if there were any differences in mortality, morbidity, and general progress. Having two different periods is not as good a control as using alternate cases, but we can definitely state that at the outset of this study in 1949, there was more severe and more frequent cross infection than we have seen for a considerable period of years.

For this study only patients admitted before the third day of life have been considered.

In the pre-aureomycin period 1947 to 1949, there were 104 cases admitted and in the 1949 to 1951 period there were 85 premature babies admitted. In the premature unit at the Hospital for Sick Children the babies are all born somewhere else, either in private homes or in other hospitals, and particularly with the latter it is the baby who is not doing well that is sent to the Sick Children's Hospital. To evaluate the effect of aureomycin, then, certain cases had to be eliminated (Table I). First, any patient who died before 3 days of age was eliminated from both groups because it was considered that these were due to congenital debility. In most cases, autopsy was held and this was substantiated. In addition, if there was any congenital abnormality, birth injury or surgical condition, proved by autopsy, these were discarded. In the control series of 104 cases, 47 died under 3 days and 9 died from congenital, surgical, or birth conditions (Table II). This left 48—of these 8

TABLE I.

	Aureomycin cases 1949 – 1951	*Controls 1947 – 1949*
Total admissions	85	104
Number who died under 3 days	31	46
Deaths after 3rd day, due to surgical complication, birth injury or congenital abnormality, proved by autopsy	7	9
Remainder	47*	48

*33 received aureomycin from third day on.
14 because of complication or lack of material started aureomycin later; all survived.

*From the Hospital for Sick Children and the Department of Pædiatrics, University of Toronto, under the direction of Alan Brown, M.D., F.R.C.P.(C.).
Read before the Canadian Society for the Study of Diseases of Children at the Annual Meeting held June 18 and 19, 1951.
†Because of shortage of material some babies did not receive it for the full period of their stay in hospital.

died from complicating infection, a mortality of 16.6%. Of the survivors, 8 suffered from infection, such as upper respiratory infection, bronchopneumonia, diarrhœa, etc. This made a total morbidity of 33.3%.

TABLE II.

CORRECTED STUDY

	Aureomycin	*Contols*
No. of cases	47*	48
Deaths	1	8
% mortality	2.1	16.6
Non-fatal infections	6†	8
Total morbidity	7†	16
% morbidity	14.9	33.3

*2 of these had cross infection gastroenteritis which failed to respond to other antibiotics, before aureomycin was started.

†1 case was admitted with a 2nd degree burn for a hot water bottle.

There were 85 cases in the aureomycin series, of these 31 died before the third day of life, and 7 died from congenital abnormalities, surgical condition or birth injury. This left 47 cases to be considered in the study—14 of these did not receive aureomycin from the start; however, it was given for some period of their stay in hospital. In some it was not given because we did not have sufficient material, early in the study, to give it. Two of the cases were those who had the gastroenteritis which prompted the study, and after failure of treatment with other antibiotics promptly recovered when aureomycin was given. These two are considered in the morbidity figures but really should be eliminated.

There was one death in the group, giving a mortality of 2.1%. Non-fatal infections, including the two mentioned above, were 6. This gave a total of 7 and a morbidity of 14.9%. If corrected for the above two cases which occurred before the use of aureomycin, it would give a morbidity of 10.6%.

To determine the effect of aureomycin on the general health, only those surviving cases who received it for their complete stay in hospital, were considered. There were 32 who received aureomycin for their whole stay in hospital and 40 controls (Table III). Birth weights showed 12 of series were under 3 lb. and 8 of the controls, so that this was not a factor in the better results.

The number of days in hospital varied with the weight at birth. The group over 4½ lb. weight averaged, for the aureomycin series of 7 cases, 26.3 days, and for the control series of 10 cases, 23.4 days; from 3½ to 4½ lb. for the aureomycin series (13 cases) 38.3 days and for the control series (22 cases) 42.9 days; from 2½ to 3½ lb. for the aureomycin series (12 cases) 56.2 days, and for the control series (8 cases) 70.9 days. On an average the discharge weights were heavier for the aureomycin group than the controls.

DISCUSSION

As previously stated our control group is not ideal in that alternate cases were not used. However, we can state that the hazard of infection was equally great during the whole period, and in the early part of the study was much greater than in any period for many years. The mortality is considerably altered and also the total morbidity.

It was our impression that the babies looked better and gained more regularly. This was

TABLE III.

SURVIVORS

	Aureomycin series				*Controls*			
	*32 Cases				40 Cases			
	Under 3 lb.	12			8			
	Over 3 lb.	20			32			
Average stay in hospital	*Days*	*Cases*	†*Weight* Lb.	Oz.	*Days*	*Cases*	†*Weight* Lb.	Oz.
Birth weight over 4½ lb.	26.3	7	5	6	23.4	10	5	3
Birth weight 3½ to 4½ lb.	38.3	13	5	3	42.9	22	5	3
Birth weight 2½ to 3½ lb.	56.2	12	5	5	70.9	8	5	0

*This number is the survivors that received aureomycin continuously from the third day, or before.

†Average discharge weight.

borne out in the smaller babies. In the larger ones, over 4½ lb. at birth, the two groups are practically the same. In the 3½ to 4½ lb. birth weight group, the average hospital stay was cut down 4½ days, and in the group 2½ to 3½ lb., it was cut down 14½ days. In addition, the babies during this period were being discharged at a higher weight so that probably all of these figures may have been increased by 2 to 4 days had the same discharge weight been observed.

CONCLUSION

Aureomycin in a dosage of 50 mgm. daily is a useful prophylactic measure against morbidity in premature babies. It also speeds growth and shortens hospital stay.

We wish to thank the Lederle Company for supplying the aureomycin for this study through the cooperation of Stanton M. Hardy, M.D.

RÉSUMÉ

Au cours de l'été de 1949 à l'Hôpital des Enfants Malades de Toronto, on observa une petite épidémie de troubles aigus de la nutrition, caractérisés par de la diarrhée, des vomissements, désydratation et toxémie. Extrêmement graves ces symptômes ne s'amendèrent pas à la thérapie ordinaire, jusqu'au moment où l'on se servit de l'auréomycine avec les plus grands succès. Les résultats s'avérèrent particulièrement heureux chez les bébés nés prématurément.

Deux groupes de prématurés furent étudiés, aux uns on donna de l'auréomycine à la dose de 50 mgm par jour et aux autres pas. On nota chez les deux groupes les différences au point de vue de la mortalité, morbidité et progrés général, en éliminant cependant ceux qui présentèrent des anomalies congénitales, des accidents de l'accouchement ainsi que des affections chirurgicales.

De ces états pathologiques 7 bébés moururent, et sur 85 cas soumis à l'auréomycinothérapie 31 ne survécurent pas la troisième journée de leur existence. Les autres, sauf un qui mourut et six qui présentèrent des infections non mortelles, gagnèrent du poids plus rapidement que les bébés non soumis au traitement. Il en est de même de leur séjour à l'hôpital qui fut beaucoup moins prolongé que celui des bébés témoins.

En somme, à la dose de 50 mgm. l'auréomycine constitue une mesure prophylactique fort utile qui tend à réduire la mortalité et à favoriser la croissance et le poids chez les prématurés.

TREATMENT OF DEHYDRATION IN INFANCY USING CONTINUOUS INTERSTITIALS AND HYALURONIDASE*

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ADMINISTRATION OF FLUIDS PARENTERALLY to the infant and young child is beset with difficulties. Because of these, fluids may be withheld until severe dehydration accompanies or enhances the original symptoms and signs of the illness. The present methods, including needling of veins and cutting down on veins, require training and practice to maintain skill, and often leave an unsightly scar. Intermittent interstitials may be given periodically during the day but these cause discomfort to the patient, are mechanically difficult in the older child and do not provide sufficient quantity of fluids.

A method of providing continuous fluid administration by interstitials using hyaluronidase to facilitate the diffusion of fluid has been tested in other centres[1, 2, 3] and described in the pædiatric literature. The practical value of this method, particularly to smaller hospitals, seemed to be of sufficient importance to warrant further study of its efficacy and a report in the general medical literature.

A series of 24 infants has been studied in whom dehydration has been corrected with fluids administered by continuous interstitial with hyaluronidase. These cases will be presented, the method of administration described, and the advantages and disadvantages of the procedure discussed.

The patients' ages ranged from 2 weeks to 19 months. Two years is considered the outside limit primarily because of the difficulty in restraining an older child. In addition, needling of veins becomes feasible over 2 years of age. The weight of the patients in the dehydrated state varies from 5 lb. 3 oz. to 25 lb. Fluid administered consisted of 2/3 5% glucose in 1/3 normal saline, 5% glucose in normal saline, Ringer's lactate, 1/6th molar lactate solution, and 5% glucose in water.

DESCRIPTION OF TECHNIQUE

The most satisfactory site for the continuous interstitial is the antero-lateral or lateral aspects of the thigh. The back and anterior abdominal wall, however, may be used.

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A special continuous interstitial tray is set up containing the following equipment: three lengths of tubing connected by a glass Y-shaped tube, with a drip bulb attached to the end of the proximal tubing, and 2 needle adapters to the ends of the distal tubings; two size 20 needles with long sharp bevels; 4 gauze squares; several cotton fluffs; two medicine glasses for iodine and alcohol; a 2 c.c. syringe and size 25 hypodermic needle; 3 clamps, and 2 towel drapes (Fig. 1).

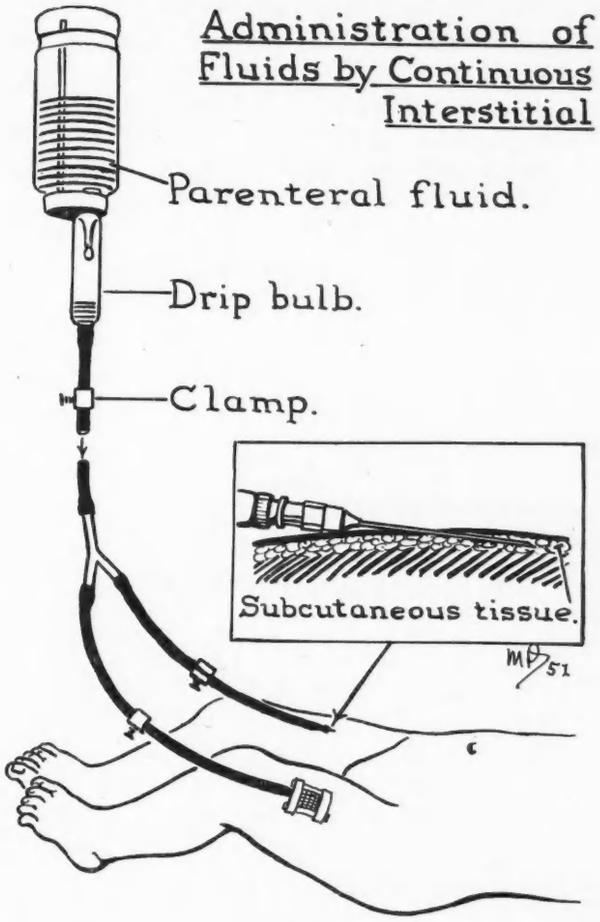

Fig. 1

The procedure is as follows: The tube system is filled with the required fluid, air bubbles dislodged, needles attached to the adapters and tubing clamped. Ankle restraints are applied. The thigh is prepared surgically with iodine and alcohol, then draped. The needles are inserted into the subcutaneous space. Gauze dressings are then applied. Sterility and maintenance of dressings is most important. This may be done by sealing off all sides of the dressing with adhesive tape or the use of a water resistant adhesive cover. The latter is advisable in the smaller infant. Our experience has shown that there is no infection if the dressings are applied carefully and kept clean and dry.

The hyaluronidase (Wydase*) is in a frozen dried state in a 2 c.c. ampoule. This readily dissolves in 1 c.c. of normal saline. One half c.c. of the hyaluronidase in solution is injected with a hypodermic needle into the rubber tubing (wiped with alcohol) just above the adapter. The clamp is removed and the hyaluronidase is carried in with the first flush of fluids. The rate of flow is then controlled by the clamp, and regulated into either thigh depending on tenseness of the swelling.

*Wydase: supplied by John Wyeth & Brother (Canada) Ltd., Walkerville, Ontario.

Hydration was re-established with "2/3 in 1/3" solution in 15 patients, with "2/3 in 1/3" solution and Ringer's lactate in 7 patients. Four patients required in addition 1/6th molar lactate solution by intravenous or continuous interstitial or blood transfusion. The shortest period an interstitial ran was 17½ hours correcting a mild dehydration before operation. The longest period was 6 days, during which time the fluids absorbed well without additional hyaluronidase. The average length of time was 1 to 2 days.

The amount of fluids administered ranged from 370 c.c. to 3,590 c.c. The rate of flow was based on the severity of dehydration and the weight of the child, similar to the rate of flow of an intravenous. In most cases, an attempt was made to provide 80 c.c. of fluid per pound of body weight per 24 hours.

With the exception of 4 infants, hydration was restored within 24 hours with weight gains of 1 to 4 lb., but the fluids were continued until hydration could be maintained on fluids by mouth. The 4 exceptions were infants who were severely dehydrated. The failure of continuous interstitial therapy in these cases will be discussed below.

Baby R.Mc. was a 2½ months old infant, weighing 5 lb. 7 oz. admitted to hospital because of severe dehydration and dystrophy. Since birth, she had been a feeding problem, the mother unable to cope with the difficulties of a cleft palate deformity. On the night of admission a continuous interstitial was started. When observed in the morning, the state of dehydration had not changed and 170 c.c. of fluids had localized in the subcutaneous space of thighs and lower abdomen. On this 2nd hospital day, an intravenous into a scalp vein was started. There was rapid improvement in the infant with absorption of fluids already collected subcutaneously and an additional 460 c.c. Intravenous fluids were continued for the 3rd, 4th and 5th days. An attempt at maintaining hydration by intermittent interstitial and fluids by mouth was continued until the 8th day. Because of a decrease in fluid intake and dehydration, continuous interstitials were restarted, with good absorption and rehydration.

The other 3 cases were similar in that fluids accumulated the first day. A scalp vein intravenous, to administer 1/6th molar lactate solution and blood, was necessary for one day only. Further hydration was carried on and maintained by continuous interstitial. These cases had one common factor, that of severe dehydration and peripheral vascular collapse. Contrary to the findings of other writers, rehydration initially was not successful by this method in this type of patient.

The electrolytes were calculated daily in several infants in this series to judge the rapidity and adequacy of correction (Tables I and II).

TABLE I.

BABY D.W.—PARENTERAL FLUID ADMINISTRATION AND DAILY BLOOD CHEMISTRY

Continuous interstitial "2/3 in 1/3" solution	*1st day 710 c.c.*	*2nd day 380 c.c 1/6th molar lactate 60 c.c.*	*3rd day I.V. blood 110 c.c. Darrow's* solution 220 c.c.*	*4th day Darrow's* solution 120 c.c.*	*5th day*
CO_2 combining power	36.1	37.7	52.9		
pH	7.28	7.38	7.5		
K	3.2	3.07	2.8	3.7	5.5
Na	140.0	134.0	135.0	138.0	135.0
Cl	112.8	108.1	100.4		
Ca	18.4	12.4			
Ph	4.6	3.3			
N.P.N.	23.1	18.0	15.3		

*2 intermittent interstitials.

Skin sensitivity.—It has been the experience of other writers[3] that 9.3% of individuals were sensitive to hyaluronidase. Positive reaction was described as a red raised area with pseudopods occurring in 5 minutes and lasting 20 to 30 minutes. In this series, intradermal skin sensitivity tests were not done before introducing hyaluronidase. There was no evidence of sensitivity reaction.

Because of the above report, a series of 50 infants and young children were tested intradermally in the following manner. One vial of hyaluronidase containing 105 turbidity units was put into solution with 1 c.c. of normal saline and then made into a 1/10th dilution. For a test dose 1/10 c.c. of this 1/10 dilution was injected intradermally into the right forearm. In a group of 19 infants, an equal amount of normal saline was used as a control. Tests were read in 15 to 20 minutes, 2 hours, and 48 hours. An additional 31 intradermal injections were done using the 1/10 hyaluronidase solution only.

In these 50 cases, there were no typical positive reactions as described by the previous author.

TABLE II.

BABY G.I.—PARENTERAL FLUID ADMINISTRATION AND DAILY BLOOD CHEMISTRY

Continuous‡ interstitial "2/3 in 1/3" and Ringer's lactate solutions	*1st day 520 c.c.*	*2nd day 1,115 c.c.*	*3rd day 640 c.c.*	*4th day 410 c.c. I.V. blood 250 c.c. Darrow's* solution 200*	*5th day interstitial R. lactate 150 c.c. Darrow's* solution 210*	*6th day interstitial "2/3 in 1/3" 70 c.c. Darrow's* solution 130 c.c.*	*7th day† "2/3 in. 1/3" 360 c.c.*	*8th day† "2/3 in. 1/3" 205 c.c.*
CO_2 combining power.		38.5	38.8	36.7	34.8	40.5		63.5
pH			7.33	7.36	7.36	7.36		7.43
K		5.05	3.3	2.85	2.45	2.85		4.5
Na		127.0	126.0	135.0	143.0	129.0		139.0
Cl		91.6	94.8	98.7	107.4	105.7		101.3
Ca		13.7	10.6	10.6	11.2	10.9		11.4
Ph		7.3	5.4	4.7	4.7	3.3		3.4
N.P.N.			55.1	30.2	19.3	17.5		28.1
Serum protein			7.6	5.53	6.6	6.34		6.37

*2 intermittent interstitials.
†3 intermittent interstitials.
‡250 c.c. vacoliters of 2/3 in 1/3 and Ringer's lactate alternated.

Baby G.I., on second hospital day, was severely dehydrated. Fluid (administered by continuous interstitial) was absorbed well from thighs. On fourth hospital day, hydration was so improved that it was maintained on fluids by mouth and additional intermittent interstitials to correct changed electrolytes.

In Baby D.W., CO_2 combining power was corrected from 37.7 vol. % to 52.9 vol. % overnight by administration of 60 c.c. of 1/6th molar lactate solution. This should be compared with Baby G.I. On 2nd day, CO_2 combining power was 38.5 vol. %. 1/6th molar lactate was withheld. Ringer's lactate and "2/3 in 1/3" solution were alternated after every 250 c.c. On 6th day, CO_2 combining power rose to 40.5 vol. % and on the 8th day to 63.5 vol. %. The more rapid response to 1/6th molar lactate solution suggests its use where possible to correct lowered CO_2 combining power.

It should be noted in both cases that the serum K level fell on 3rd and 4th days, and was corrected by intermittent interstitials of Darrow's solution. The calcium and phosphorus ratios remained normal. In both cases N.P.N. was elevated in dehydrated state, returning to normal with hydration.

DISCUSSION

Hyaluronidase is an enzyme that depolymerizes hyaluronic acid thus changing it from a gel to a less viscous substance. In 1934, the discovery was made[4] that the formed elements of intercellular substance are embedded in an amorphous ground substance. Four years later on the basis of chemical studies, Meyers called

this substance a mucopolysaccharide present in the physical state of a gel and known as hyaluronic acid.[5] At an earlier date, from animal experiments, a "spreading factor" was found to exist in mammalian testicular tissue.[6] Later experiments demonstrated its presence in bacteria,[7] spermatozoa,[8, 9] leech extracts,[4] bee, snake and spider venoms.[4, 11] Through bacterial experiments, Meyers found that this "spreading factor" depolymerized hyaluronic acid, making it less viscous. The enzyme was called hyaluronidase.[12] Chain and Dutchie in 1939 reidentified the spreading factor of Duran-Reynals as hyaluronidase.

Sannella is credited with the vision of the clinical adaptation of hyaluronidase as an aid in parenteral fluid administration.[1] Sannella, Hechter, and Schwartzman[1, 2, 3] have tested hyaluronidase for its favourable and deleterious effect on laboratory animals and then man. The first two writers checked blood count, blood pressure and pulse, and found no abnormality. Hechter pointed out that absorption of fluids with hyaluronidase was accelerated 12 times, a wider field of absorption channels being put to use.

Schwartzman demonstrated no alteration in body physiology after examinations of urine, blood count and sedimentation rate, and completion of chemical tests for cholesterol, phosphorus, proteins, urea nitrogen, creatinin, sugar, icteric index, Van den Bergh and cephalin flocculation. Infection was not enhanced. The fluids they used consisted of 5% glucose in normal saline, Ringer's lactate, plasma, and blood. In our series plasma and blood were not used.

The principal advantage of this technique is the ease of administration. No technical skill other than sterile technique is required. The hydration and electrolyte balance can be restored in most cases as quickly as by intravenous route. There is also less danger of over hydration. As hydration is re-established and less fluids absorbed from the interstitial site, the pressure of fluid at the site increases to the degree of limiting fluids. This latter observation must be differentiated from the lack of absorption due to the stage of peripheral vascular collapse.

If the site of injection is not prepared surgically and care taken to keep dressings dry and clean, infection with abscess formation is a real risk. Such an unfortunate event did not occur in our series.

SUMMARY AND CONCLUSIONS

1. Method of setting up a continuous interstitial using hyaluronidase has been described.

2. Hydration and electrolyte balance are reestablished in most cases as quickly by this method as by intravenous therapy.

3. A severely dehydrated patient in peripheral vascular collapse requires intravenous fluids during the first 24 hours for correction of the vascular collapse. Continuous interstitials may then carry on the rehydration process.

4. Infection is not a disadvantage if sterile technique is used and dressings maintained dry and clean.

5. Skin tests for sensitivity to hyaluronidase on 50 infants showed no typical positive reactions.

6. This method of administering fluids is particularly useful in small hospitals.

Grateful acknowledgment of help and advice is expressed to Dr. Margaret Mullinger and Dr. H. E. Edwards.

REFERENCES

1. SANNELLA, L. S.: *Yale J. Biol. & Med.*, **12**: 433, 1940.
2. HECHTER, O. AND DOPKEEN, S. K.: *J. Pediat.*, **30**: 645, 1946.
3. SCHWARTZMAN, J. *et al*: *J. Pediat.*, **33**: 267, 1948.
4. BENSLEY, S.: *Anat. Rec.*, **60**: 93, 1934.
5. MEYER, K.: Cold Spring Harbour Symposium on Quantitative Biology, **6**: 91, 1938.
6. DURAN-REYNALS, F.: *J. Exper. Med.*, **50**: 327, 1929.
7. *Idem*: *J. Exper. Med.*, **58**: 161, 1933.
8. MCCLEAN, D.: *J. Path. & Bact.*, **34**: 459, 1931.
9. CHAIN, E. AND DUTHIE, E. S.: *Nature*, **144**: 977, 1939.
10. *Idem*: *Brit. J. Exper. Path.*, **21**: 324, 1940.
11. DURAN-REYNALS, F.: *J. Exper. Med.*, **69**: 69, 1937.
12. MEYER, K.: *Proc. Soc. Exper. Biol. & Med.*, **34**: 816, 1936.

Solitary gallstones are often thought to be harmless and are apt to be dismissed as unimportant findings if they are not producing symptoms. The close correlation between the incidence of solitary stones in a series of 387 consecutive cases of patients operated on at the Presbyterian and Women's Hospitals, Philadelphia, with a final diagnosis of cholelithiasis, all of which were symptomatic, and the incidence of asymptomatic solitary stones in another series suggests that they are just as prone to produce symptoms as are their multiple counterparts. Furthermore, they produce the same signs and symptoms with about the same degree of frequency, and cause the same complications.—R. S. Mechling and J. R. Watson, *Surg., Gynec. & Obst.*, October, 1950.

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THIAMIN THERAPY IN NEURO-PSYCHIATRY*

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A PHYSICIAN named Jacobus Bontius in 1642 described a disease which was known to the natives of Java as beriberi. Another disease, known to the peasants of Lombardy as pellagra (meaning rough skin), was described by the Italian physician Frapolli in 1771. Each of these conditions had been known to the populace of different areas for many years prior to their appearance in medical literature. During the nineteenth century both diseases were reported in many countries, and a number of theories were advanced as to their etiology. Dietary methods of prevention and treatment were employed successfully in some instances. However, it was not until 1897 that Eijkmann observed that a form of paralysis occurring in fowls (polyneuritis gallinarum) was cured by feeding them whole rice, or rice bran, in place of polished rice. This observation led to the discovery of a number of highly potent substances, which must be present in small quantities in every diet if health was to be maintained. Deficiency of one of these vitamins in the diet was found to result in the development of a characteristic clinical syndrome, which could be cured by administration of small amounts of the vitamin.

During the first part of this century vitamin B, contained in yeast, rice polish, liver, etc., was believed to be a single substance, but in 1926 a thermolabile component was distinguished, and from it was isolated vitamin B_1 (thiamin) which is curative of beriberi. The efficacy of thiamin in the treatment of beriberi, and the assumption that a prolonged deficiency of vitamin B_1 in man will lead to peripheral neuritis, led before long to a therapeutic trial of this substance in many other types of neuritis.

Cobb and Coggeshall[1] in 1934 grouped the principal causes of peripheral neuritis under six headings:

Localized neuritis: (1) Mechanical (*e.g.*, pressure, trauma, Volkmann contracture). (2) Infections (*e.g.*, diphtheria, streptococcal, tetanus, leprosy).

Generalized polyneuritis: (3) Virus (*e.g.*, measles, smallpox, herpes, poliomyelitis, encephalomyelitis). (4) Bacteriotoxic (*e.g.*, streptococcal infections, gonorrhœa, meningitis, typhoid, typhus, pneumonia, malaria, relapsing fever, syphilis). (5) Chemical (*e.g.*, heavy metals, metalloids, alcohols, many organic compounds). (6) Nutritional deficiency, or metabolic (*e.g.*, pellagra, beriberi, pernicious anæmia, diabetes, myxœdema, chronic colitis, wasting diseases).

Aring and Spies[2] in 1939 considered the effect of thiamin therapy on these different types of neuritis, and the conclusions they then reached have been substantially borne out by widespread therapeutic application since this time. In the treatment of localized neuritis due to mechanical causes or infections, the results of different workers have been conflicting, but there has been definite evidence of benefit in a number of instances. The virus group appears to be unaffected by thiamin. In the bacteriotoxic group, polyneuritis is probably the result of a relative deficiency of thiamin, and improved nutrition accounts for the rarity with which neuritis develops during these infections nowadays, even in those rare instances where antibiotics have not procured a dramatic reduction in intensity and duration of symptomatology. In polyneuritis due to chemical poisons, large amounts of thiamin, given over a prolonged period, may hasten recovery, although thiamin deficiency is believed to play no part in the onset of the condition. In most of the cases of polyneuritis associated with nutritional deficiencies or metabolic disorders, thiamin is effective, although prolonged administration of large doses may be necessary, and even then recovery only partial.

The rôle of thiamin in the therapy of many types of peripheral neuritis has been outlined above. In addition, this substance was soon utilized, with varying degrees of success, in the treatment of a number of other syndromes commonly encountered in the practice of neuropsychiatry.

In 1881, Wernicke,[3] on the basis of three patients studied during life and at the autopsy table, described a syndrome characterized by clouding of consciousness, varying ophthalmoplegias, and ataxia. In 1938, Alexander, Myerson and Pijoan[4] were able to produce Wernicke's pseudo-encephalitis in the pigeon by the feeding of diets low in vitamin B_1 and high in other vitamins, and Alexander was able to show the identity of these experimental lesions, with the lesions of hæmorrhagic polioencephalitis occurring in chronic alcoholism in man. Campbell and Biggart[5] pointed out that a significant number of these cases occurred in non-alcoholics, and Jolliffe *et al.*[6] reported on 34 cases of Wernicke's disease, three of which were in non-

*From a paper read before the Vancouver Medical Association, Section of Neurology and Psychiatry, on April 2, 1951.

alcoholics. The latter group of workers found that the ophthalmoplegia of Wernicke's disease is due to a deficiency of, and responds to, thiamin. The clouding of consciousness in some instances responds to thiamin and not to nicotinic acid, and in other instances responds to nicotinic acid and not thiamin. In still other cases it responds to neither, but to large doses of the entire vitamin B complex.

In the case of Korsakoff's psychosis, the rôle of thiamin is not defined so precisely as in the case of Wernicke's syndrome, and a number of physicians have questioned the value of therapy with this compound. However, other workers in this field[7, 8] were convinced of the close relationship between the psychosis and vitamin B_1 deficiency. Caldwell and Hardwick[9] reported that prolonged administration of thiamin may benefit the organic mental symptoms, or the polyneuropathy, or both, and this opinion has been upheld by the experience of many other physicians. Failure of this form of treatment in some patients with Korsakoff's syndrome has been explained by postulating that in these cases irreversible structural changes have already occurred.

It has been shown that vitamin B_1 deficiency is responsible for some of the neuro-psychiatric complications of chronic alcoholism, and Moore[10] has pointed out that the symptoms of deficiency arise from inadequate nutrient intake, not from alcohol itself. Now it is known that polyneuritis, Wernicke's encephalopathy and Korsakoff's psychosis may each result from chronic excessive consumption of alcohol, and thiamin has been widely used in the treatment of all these conditions. It is therefore not surprising that this substance has been used in the treatment of many other manifestations of the toxic effects of alcohol. Benefit has been reported in the treatment of delirium tremens, and other psychoses precipitated by alcohol, though there does not appear to be any incontrovertible evidence that the vitamin B complex is related to their pathogenesis. Latterly it has been observed that a large proportion of chronic alcoholics show hypoadrenocorticism, and a number of the symptoms and complications of alcoholism have been attributed to a deficiency of adrenocortical hormones. Perhaps it is permissible to digress briefly on this subject.

In 1946, Selye[11] reported that certain stimuli, such as worry or grief, together with alcohol, will produce hypertrophy of the adrenal cortex, but will eventually lead to hypoadrenocorticism. Lloyd and Williams[12] have shown there is usually a decrease in lipoid content of the adrenals, in cases of alcoholic cirrhosis examined at autopsy. Bowman, Wortis and co-workers found depression of the glucose tolerance curve in alcoholic patients, with improvement after one week of hospitalization. Tintera and Lovell[13] distinguished between two groups of alcoholic patients—those with primary or constitutional hypoadrenocorticism, and those in whom adrenal hypofunction was secondary to alcoholism. They observed that 17-ketosteroids and androgens were frequently low, and that hypoglycæmia was universal following withdrawal of alcohol—the average fasting blood sugar level in their series being only 60.9 mgm. per 100 c.c. They found that administration of adrenocortical extract restored the blood sugar to the normal level, and relieved the unpleasant symptoms of withdrawal of alcohol. Some physicians have also observed dramatic improvement in patients with delirium tremens following administration of adrenocortical hormones.

So far, a number of conditions have been discussed in which thiamin therapy is commonly considered to be indicated, although in some of these syndromes deficiency of thiamin does not appear to be the causative factor. However, probably the earliest and most frequent manifestation of thiamin deficiency is none of the conditions hitherto discussed, but that of neurasthenia. In 1939, Jolliffe and co-workers[14] at the Bellevue Hospital reported on the experimental production of vitamin B_1 deficiency in normal subjects, and their work was confirmed and extended by Williams, Mason, Wilder, and other workers[15] at the Mayo Clinic. In well-controlled experiments in normal human subjects, the latter group of investigators were able to produce the characteristic syndrome of neurasthenia. Other groups of workers[16, 17] measured the increased fatiguability, and diminished work output of subjects with experimentally induced vitamin B_1 deficiencies. Ancel Keys and co-workers[18] observed mental deterioration with apathy, depression, and hypochondriasis in young men deprived of vitamin B complex. More recently, Kreisler, Liebert and Horwitt[19] observed the effects of induced vitamin B complex deficiency in psychotic patients, and concluded that it caused severe primary mental changes, or aggravation

of pre-existing psychotic trends among the psychotic subjects.

Having considered the value of thiamin in the treatment of the conditions so far enumerated, it is now possible to reach some conclusions as to the indications for therapy with this substance. For some time it has been recognized that deficiency of vitamin B_1 leads progressively to: (1) a neurasthenic syndrome, (2) involvement of peripheral nerves, (3) involvement of midbrain and neighbouring structures. If administered before irreversible structural changes have occurred, thiamin therapy is effective in each of these conditions, and it is also of value in a number of cases of peripheral neuritis where other etiology is demonstrable. The efficacy of thiamin in the treatment of alcoholic peripheral neuritis, Wernicke's encephalopathy, and Korsakoff's psychosis, has already been discussed; and it has been noted that symptoms of vitamin B_1 deficiency occurring in alcoholics result from inadequate nutrient intake—not from the alcohol itself. The rôle of thiamin in the treatment of other toxic manifestations and complications of alcoholism requires further investigation, and it appears that other therapeutic agents may be of greater value in controlling them than thiamin. Nevertheless, some degree of thiamin deficiency must exist in every instance of prolonged ingestion of alcohol, and it appears justifiable to administer thiamin in each case, in addition to instituting such other measures as may be necessary.

In order that therapy may be effective, it is essential that individual dosage, frequency and route of administration, and duration of treatment, are each considered. Jolliffe[20] has recommended doses varying from 10 to 30 mgm. daily in neurasthenia, to 50 to 100 mgm. three times daily in Wernicke's syndrome, with doses of 50 to 100 mgm. daily sufficing for conditions intermediate in severity. In each instance parenteral administration was recommended, and the author stressed the fact that a trial of therapy should extend over three months in the case of those conditions which have been present this length of time or longer. Although parenteral administration—or a combination of parenteral and oral administration—is still mandatory in the initial treatment of all the more severe syndromes, some physicians consider oral administration of 50 to 100 mgm. daily for at least three months to be effective in a number of cases of neurasthenia.

REFERENCES

1. COBB, S. AND COGGESHALL, H. C.: *J. A. M. A.*, **103**: 1608, 1934.
2. ARING, C. D. AND SPIES, T. D.: *J. Neurol. & Psychiat.*, **2**: 335, 1939.
3. WERNICKE, C.: Lehrbuch der Gehirnkrankheiten für Aertze und Studierende, Berlin, T. Fischer, vol. 2., p. 229, 1882.
4. ALEXANDER, L., MYERSON, A. AND PIJOAN, M.: *Tr. Am. Neurol. A.*, **64**: 135, 1938.
5. CAMPBELL, A. C. P. AND BIGGART, J. H.: *J. Path. & Bact.*, **48**: 245, 1939.
6. JOLLIFFE, N., WORTIS, H. AND FEIN, H. D.: *Arch. Neurol. & Psychiat.*, **46**: 569, 1941.
   WORTIS, H., BEUDING, E., STEIN, M. H. AND JOLLIFFE, N.: *Arch. Neurol. & Psychiat.*, **47**: 215, 1942.
7. ROSENBAUM, M. AND MERRITT, H. H.: *Arch. Neurol. & Psychiat.*, 41: 978, 1939.
8. WEISS, S.: Cecil's Textbook of Medicine, W. B. Saunders Co., p. 602, 1941.
9. CALDWELL, W. A. AND HARDWICK, S. W.: *J. Ment. Sc.*, **90**: 95, 1944.
10. MOORE, N. S.: *New York State J. Med.*, January 15, 1949.
11. SELYE, H.: *J. Clin. Endocrinol.*, **6**: 153, 1946.
12. LLOYD, C. W. AND WILLIAMS, R. H.: *Am. J. Med.*, **4**: 315, 1948.
13. TINTERA, J. W. AND LOVELL, H. W.: Paper read at the Annual Meeting, American Geriatrics Society, Atlantic City, N.J., on June 4, 1949.
14. JOLLIFFE, N., GOODHART, R., GENNIS, J. AND CLINE, J. K.: *Am. J. M. Sc.*, **198**: 198, 1939.
15. WILLIAMS, R. D., MASON, H. L. AND SMITH, B. F.: *Proc. Staff Meet., Mayo Clin.*, **14**: 787, 1939.
    WILLIAMS, R. D., MASON, H. L., WILDER, R. M. AND SMITH, B. F.: *Arch. Int. Med.*, **66**: 785, 1940.
    WILLIAMS, R. D., MASON, H. L., SMITH, B. F. AND WILDER, R. M.: *Arch. Int. Med.*, **69**: 721, 1942.
    WILLIAMS, R. D., MASON, H. L., POWER, M. H. AND WILDER, R. M.: *Arch. Int. Med.*, **71**: 38, 1943.
16. JOHNSON, R. E., DARLING, R. C., FORBES, H. W., BROUHA, L., EGANA, E. AND GRAYBEIL, A.: *J. Nutrition.*, **24**: 585, 1942.
17. BARBORKA, C. J., FOLTZ, E. E. AND IVY, A. C.: *J. A. M. A.*, **122**: 717, 1943.
18. KEYS, A. *et al.*: *Am. J. Physiol.*, **144**: 5, 1945.
19. KREISLER, O., LIEBERT, E. AND HORWITT, M. K.: *Am. J. Psychiat.*, **105**: 107, 1948-49.
20. JOLLIFFE, N.: *J. A. M. A.*, **117**: 1496, 1941.

TRAITEMENT A LA THIAMINE EN NEURO-PSYCHIATRIE

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UN MÉDECIN du nom de Jacobus Bontius décrivit en 1642 une maladie que les habitants de Java appelaient le béribéri. En 1771 le médecin italien Frapolli décrivit une autre maladie connue des paysans de la Lombardie sous le nom de pellagre (qui signifie peau rude). Chacune de ces affections était connue de la population de diverses régions longtemps avant qu'on en fit mention dans la littérature médicale. Au cours du dix-neuvième siècle ces deux maladies parurent dans plusieurs pays et leur étiologie suscita diverses théories. Dans certains cas on eut recours avec succès à des traitements préventifs et curatifs à base de régimes alimentaires. Mais ce ne fut qu'en 1897 que Eijkmann remarqua qu'une paralysie à forme polynévritique chez des poules guérissait par le seul fait de les alimenter au

riz entier ou au son de riz au lieu de riz décortiqué. Cette observation conduisit à la découverte d'un certain nombre de substances de haute valeur, dont la présence en petites quantités dans chaque régime alimentaire est indispensable au maintien de la santé. Une de ces vitamines venait-elle à manquer qu'il se produisait un syndrôme clinique caractéristique, que l'emploi d'une petite quantité de la vitamine guérissait.

Au cours du premier quart de notre siècle on crut que la vitamine B, présente dans la levure, le riz cortiqué, le foie, etc. était une substance isolée, mais en 1926 on découvrit un composant thermolabile dont fut tirée la vitamine B_1 (thiamine) qui guérit le béribéri. L'efficacité de la thiamine dans le traitement du béribéri et la présomption qu'une carence prolongée de vitamine B_1 entraînera une névrite périphérique, voilà autant de raisons qui ont prévalu pour tenter l'essai de la thiamine dans beaucoup d'autres formes de névrite.

En 1934 Cobb et Coggeshall divisèrant les principales causes de névrite périphérique en six grandes variétés:

Névrite localisée: (1) Mécanique (compression, traumatisme, contracture de Volkmann). (2) Infections (diphtérie, streptococcies, tétanos, lèpre).

Polynévrite généralisée: (3) Virus (rougeole, variole, herpès, poliomyélitis, encéphalomyélite). (4) Microbienne (infections streptococciques, gonorrhée, méningite, typhoïde, typhus, pneumonie, malaria, syphilis). (5) Chimique (métaux lourds, métalloïdes, alcools, maints composés organiques). (6) Insuffisance de la nutrition ou du métabolisme (pellagre, béribéri, anémie pernicieuse, diabète, myxœdème, colite chronique, maladies carentielles).

En 1939 Aring et Spies étudièrent l'effet du traitement à la thiamine sur ces différentes formes de néphrites, et depuis ce temps un emploi de plus en plus répandu de la médication prouve davantage tous les jours le bien fondé de leurs observations. Dans le traitement de la névrite localisée relevant de causes mécaniques ou d'infections, différents cliniciens ont obtenu des résultats contradictoires, mais nombreux furent les cas où ils s'avérérent satisfaisants. La thiamine semble inactive dans les infections à virus. Dans le groupe des maladies microbiennes il est probable que la polynévrite résulte d'une certaine carence en thiamine, si l'on en juge par la rareté de cette complication lorsque le régime alimentaire est amélioré, même dans ces cas peu fréquents où la durée et l'intensité des symptômes n'ont pas cédé devant la remarquable action des antibiotiques. Dans la polynévrite causée par des poisons chimiques, que l'on ne croit pas d'ailleurs dépendre d'une carence vitaminique, on observe un retour rapide à la normale lorsque la thiamine est donnée à hautes doses pendant longtemps. C'est encore à cette condition, bien qu'ici la guérison ne peut être que partielle, que la thiamine s'avère efficace dans tous les cas de polynévrite associés à des troubles de la nutrition ou du métabolisme.

En outre de son efficacité dans ces formes de polynévrite, la thiamine fut employée bientôt, avec des succés variables, dans un certain nombre d'autres syndrômes que l'on rencontre couramment dans la pratique de la neuro-psychiâtrie.

Après avoir étudié trois de ses malades de leur vivant ainsi que sur la table d'autopsie, Wernicke décrivit en 1881 un syndrôme caractérisé par une confusion de la conscience, des ophthalmoplégies à divers degrés et de l'ataxie. En 1938 Alexander, Myerson et Pijoan réussirent à produite la pseudo-encéphalite de Wernicke chez le pigeon en le nourissant d'aliments dont la teneur était basse en vitamine B_1 et élevée en autres vitamines, et Alexander put démontrer que ces lésions expérimentales étaient identiques à celles de la polioencéphalite hémorragique que l'on observe chez l'alcoolique chronique. Campbell et Biggart soulignèrent la présence de ces lésions chez un bon nombre de non alcooliques, et sur 34 cas de maladie de Wernicke rapportés par Jolliffe trois autres n'étaient pas alcooliques. On nota que dans cette affection l'ophthalmoplégie dépendait d'une carence en thiamine, et aussi qu'elle guérissait grâce à la thiamine. Dans certains cas l'obnubilation de la conscience cédait à la thiamine mais non pas à l'acide nicotinique, dans d'autres c'était le contraire; dans d'autres cas enfin, ni l'une ni l'autre n'agissaient et seules des doses élevées de complexe vitaminique B s'avéraient efficaces.

L'action de la thiamine ne se manifeste pas aussi nettement dans la psychose de Korsakoff que dans le syndrôme de Wernicke, au point que plusieurs médecins ont mis en doute sa valeur thérapeutique. D'autres cliniciens cependant virent une relation étroite de cause à effet entre la carence de vitamine B_1 et la psychose. Caldwell et Hardwick, et à leur suite de nombreux autres médecins, ont émis l'opinion que l'emploi

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prolongé de la thiamine peut améliorer les symptômes organiques, ou la polyneuropathie, ou les deux à la fois. Dans les cas d'insuccès de cette thérapie chez certains malades atteints de la psychose de Korsakoff, il fallait chercher la cause dans les altérations organiques préexistantes.

On a fait la preuve que la carence de vitamine B_1 est à l'origine de quelques-unes des complications neuro-psychiâtriques de l'alcoolisme chronique, et Moore a souligné que ce n'est pas l'alcool lui-même mais bien le régime alimentaire déficient qui provoque les symptômes de carence. On sait maintenant que le polynévrite, l'encéphalopathie de Wernicke et la psychose de Korsakoff peuvent toutes les trois résulter de l'alcoolisme chronique avéré, et la thiamine a été largement utilisée pour traiter ces affections; rien d'étonnant non plus qu'elle ait servi au traitement de nombre d'autres manifestations des effets toxiques de l'alcool. Bien qu'il ne soit pas prouvé hors de tout doute que le complexe de la vitamine B entre dans la pathogénie du déliriums tremens et d'autres psychoses engendrées par l'alcool, ces affections ont été traitées avec succès par la thiamine. Il a aussi été montré récemment que nombreux sont les alcooliques chroniques chez qui la fonction du cortex surrénalien est déficiente, si bien qu'on attribue à une insuffisance de ces hormones quelques-uns des symptômes et des complications de l'alcoolisme. Ainsi une brève digression à ce sujet ne serait point oiseuse.

En 1946 Selye rapporta que certains stimuli tels que l'anxiété ou le chagrin, en même temps que l'alcool, vont produire d'abord une hypertrophie mais eventuellement à la longue une atrophie du cortex surrénalien. Dans les cas de cirrhose alcoolique Lloyd et Williams ont montré à l'autopsie que la teneur en lipoïdes des surrénales était diminuée. Bowman et Wortis notèrent une chute de la courbe de tolérance au glucose chez leurs malades alcooliques, mais avec redressement après une semaine d'hospitalisation. Tintera et Lovell font une distinction entre deux groupes d'alcooliques—ceux chez qui l'hypofonctionnement cortico-surrénalien était primitif ou constitutionnel, et ceux chez qui il était secondaire à l'alcoolisme. Ils remarquèrent la basse proportion d'androgènes, ainsi que la fréquence de l'hypoglycémie faisant suite à la suppression de l'alcool—à piene 60.9 mgm. par 100 c.c. comme niveau moyen du sucre dans la sang à jeun. Ils notérent que l'emploi d'extrait cortico-surrénalien ramenait le sucre sanguin à son niveau normal, et calmait les malaises pénibles de la suppression de l'alcool; de telles hormones ont parfois aussi opéré de véritables transformations chez des malades en proie au délirium tremens.

Il a été question jusqu'ici d'affections qui bien que ne paraissant pas être causées par une carence de thiamine n'en sont pas moins soulagées par cette même substance. Parmi toutes ces affections cependant il n'en n'est pas qui se soit avérée l'une des plus fréquentes et précoces manifestations de la carence de thiamine que la neurasthénie. En 1939, Jolliffe à l'Hôpital Bellevue, Williams, Mason et Wilder à la Clinique Mayo, rapportèrent respectivement leurs observations sur la production expérimentale de la carence de vitamine B_1 chez des sujets normaux, et ces derniers, à la suite d'expériences bien contrôlées, purent produire le syndrôme caractéristique de la neurasthénie. D'autres cliniciens purent chez de pareils sujets mesurer l'augmentation de la fatigabilité et l'amoindrissement du rendement au travail. Ancel Keys et ses collègues observèrent de la détérioration mentale avec apathie, dépression et hypochondrie chez des jeunes hommes privés de complexe de vitamine B. Une telle carence provoquée chez des malades atteints de psychoses a permis à Kreisler, Liebert et Horwitt de conclure qu'elle détermine soit des altérations mentales primitives graves soit une aggravation de troubles psychiques préexistants.

La valeur thérapeutique de la thiamine ainsi établie, on peut dès lors en poser les indications. C'est un fait acquis déjà depuis quelque temps que la carence de vitamine B_1 conduit pregressivement à: (1) un syndrôme neurasthénique, (2) une atteinte des nerfs périphériques, (3) une atteinte des noyau centraux du cerveau et des tissus environnants. Dans chacun de ces cas la thiamine est efficace si elle est donnée avant que ne se produisent des lésions organiques irréparables, et elle agit bien également dans de nombreux cas de névrite périphérique qui relèvent d'une étiologie différente. Nous savons déjà que la thiamine rend de grands services dans la névrite périphérique alcoolique, l'encéphalopathie de Wernicke et la psychose de Korsakoff; il a été fait mention aussi que les symptômes de carence de vitamine B_1 survenant chez les alcooliques viennent non pas de l'alcool lui-même mais d'une alimentation inadéquate. Le rôle de

la thiamine dans le traitement d'autres manifestations toxiques et complications de l'alcoolisme vaut qu'on en fasse une étude plus poussée, et il se peut que d'autres agents thérapeutiques finissent par s'avérer encore plus efficaces que la thiamine. Néanmoins comme l'ingestion prolongée d'alcool s'accompagne d'un certain degré de carence de thiamine, on semble justifiable de prescrire cette substance dans chaque cas, en outre de préconiser les autres médications que s'imposent.

Pour que le traitement soit efficace il est essentiel de prendre en considération la posologie individuelle, la voie d'administration et la durée du traitement. Jolliffe recommande des doses variant de 10 à 30 mgm. par jour dans la neurasthénie, de 50 à 100 mgm. trois fois par jour dans le syndrôme de Wernicke, avec des doses de 50 à 100 une fois par jour dans les cas intermédiaires. La voie parentérale est recommandée dans chaque cas, et l'auteur recommande de prolonger l'essai thérapeutique au-delà de trois mois dans les cas où ces maladies durent déjà depuis cette période de temps ou davantage. Bien que la voie parentérale—seule ou combinée à la voie orale—soit encore de règle dans le traitement initial des syndrômes les plus graves, certains médecins considèrent que l'administration par la bouche de 50 à 100 mgm. de thiamine par jour pendant au moins trois mois agit bien dans un bon nombre de cas de neurasthénie.

CHLOROMYCETIN IN THE TREATMENT OF MUMPS

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DURING THE SUMMER of 1950, a report was observed in the medical literature in which it was stated that chloromycetin was considered to have a pronounced beneficial effect on the course of mumps. At that time, two patients ill with mumps orchitis were admitted to the Alexandra Hospital, and both these patients were given chloromycetin as specific therapy for mumps, particularly in an attempt to relieve their distress from the orchitis. It was with some surprise, and considerable disappointment, that no beneficial effects were observed, and their illnesses proceeded to run the usual unpleasant clinical course.

It was considered that possibly these patients may have been exceptions to a usual response, therefore, it was decided to determine, whether or not, chloromycetin would hasten the subsidence of swelling of the salivary glands in mumps, shorten the clinical course, and prevent common complications of this disease, *e.g.*, orchitis, meningitis.

The plan of treatment was to give chloromycetin,* 2.5 gm./sq.m. of body surface, *i.e.*, 4 grams for an adult, in 4 equal daily doses for 5 days, to each patient ill with mumps, and to observe the effect in regard to the well-being of the patient, time for subsidence of swelling of the salivary glands and shortening of the clinical course, the prevention of "complications" and therapeutic benefit on those patients who had orchitis at the time of admission to hospital.

In all, 57 consecutive cases of mumps, uncomplicated with other diseases, were treated. Four patients who were ill with lymphosarcoma, sarcoma of the bladder, cerebral palsy, and gastric ulcer, respectively, were not treated because of the possibility of a mistaken diagnosis or intolerance to the drug.

In the children, ages 1 to 15 years, the disease was mild, causing little discomfort, this being the usual course of mumps in childhood. Nevertheless, there was no dramatic subsidence of the swelling of the salivary glands in any of the children, the disease running a course identical with that in children not receiving chloromycetin. Likewise, "complications" from mumps are uncommon in children, and the fact that no complications were noted among twenty-five children who were given chloromycetin, is of little significance in so small a number. Nevertheless, in the older age groups, mumps may be quite unpleasant. In this group, the administration of chloromycetin also, did not cause any apparent decrease in the time of subsidence of swelling of the salivary glands. Furthermore, three patients who had associated orchitis, continued to experience severe pain, and again, there was no apparent decrease in the time for the subsidence of testicular inflammation, and in particular, no dramatic subsidence during the 5

*A supply of chloromycetin (Chloramphenicol, Parke-Davis) was donated for this study through the generosity of R. D. Buckman, M.D., Director, Department of Therapeutic Development, Parke-Davis Co., Walkerville, Ont.

days of therapy. The clinical course of these patients with orchitis exhibited no obvious dissimilarity from that of patients with orchitis who had not received chloromycetin. A fourth patient developed orchitis on the 4th day of chloromycetin administration.

Four females who had swelling of the salivary glands, but who were afebrile, developed fever 102 to 104° and signs of meningeal irritation during chloromycetin administration. Examination of their cerebro-spinal fluid revealed findings consistent with a diagnosis of mumps meningitis.

Fall in temperature was considered to be an unreliable criterion for evaluation of these cases. Frequently, the elevated temperature did fall to normal within 24 to 48 hours after chloromycetin administration. Nevertheless, this fall in temperature is usually observed regardless of the administration of chloromycetin. Furthermore, many of the patients were afebrile at the time of admission.

No intolerance to chloromycetin was noted in any of the patients.

COMMENT

Contrary to a previous report in the medical literature, the administration of chloromycetin as a specific form of therapy was of no apparent benefit to these persons ill with mumps. There was no observable decrease in the swelling of the salivary glands, dramatic or otherwise. More important still, there was no unusual decrease in the inflammation of orchitis, or relief from pain in this distressing aspect of mumps. Furthermore, chloromycetin failed to prevent mumps meningitis and mumps orchitis as complications of the disease. Presumably, mumps is a generalized infection, the virus being disseminated throughout the body, and the so-called "complications" are only clinical manifestations of this generalized infection. Nevertheless, it is interesting to note that all cases of mumps do not have a pleocytosis in the cerebro-spinal fluid. Two of the patients who developed meningitis had close contact with one another, and it may well be that they both were infected with a common neurotrophic strain.

Whereas chloromycetin distinctly failed in this limited number of cases to exert a decidedly favourable influence on the course of mumps, a further clinical trial on a larger number of patients was considered to be unwarranted.

SUMMARY

1. Chloromycetin was given to 57 consecutive cases of mumps that were uncomplicated by other diseases, and it failed to exert any apparent favourable influence on the clinical course of this disease.

2. Chloromycetin failed to prevent orchitis or meningitis as "complications" of mumps.

3. Chloromycetin failed to relieve the distressing symptoms of mumps orchitis or cause any definite diminution of inflammatory signs in that disease.

REFERENCE

1. CHALIONGUI, P.: Chloromphenicol in Mumps, *Lancet*, **2**: 75, 1950.

TABLE I.

Age	0 to 1 yr.		2 to 8 yrs.		9 to 15 yrs.		16 to 20 yrs.		21 to 25 yrs.		26 to 30 yrs.	
Sex	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Number	–	2	13	8	0	2	2	6	6	9	6	3

TABLE II.

Age	*Orchitis*	*Day of onset of orchitis*	*Disappearance of gross swelling*	*C.S.F.*
19 yr.	bilateral	2nd day of disease	16 days	neg.
25 yr.	bilateral	6th day of disease	10 days	neg.
22 yr.	right	4th day of therapy	11 days	—
29 yr.	right	7th day of disease	9 days	—

TABLE III.

Age	*Onset of fever and meningeal signs*		*C.S.F. examination*			
			Protein mgm. %	*Sugar mgm. %*	*Chloride mgm. %*	*Cells*
20 yr.	7th day of illness	2nd day of therapy	162.5	56	437	230 (L223) (P7)
20 yr.	5th day of illness	3rd day of therapy	106.0	61	448	500 (L)
15 yr.	8th day of illness	4th day of therapy	66.2	50	435	600 (L)
19 yr.	5th day of illness	5th day of therapy	36.2	46	426	49 (L44) (P5)

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OUR PRESENT KNOWLEDGE OF POTASSIUM IN PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES*

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IN RECENT YEARS much attention has been directed to the rôle of potassium in physiological states as well as in certain pathological conditions. At intervals, reviews have appeared[1 to 7] which have been limited to certain specific phases of the subject. This paper is offered to present more fully our present knowledge of potassium in normal and pathological states.

PHYSIOLOGY OF POTASSIUM

Distribution.—Potassium functions chiefly as an intracellular cation. As such it has an important function in acid-base balance. It is not, however, as previously thought, fixed within the cell. There is normally some potassium in the extracellular compartment and in certain abnormal conditions sodium may enter the tissue cells and replace potassium. With growth and repair of tissue, potassium is taken into the cell, and with utilization or degeneration of protoplasm it leaves the cell. Thus, a constant shifting back and forth across the cell membrane takes place which is probably most influenced by disturbances of acid-base equilibrium.

Most of the body potassium is present within the cells. It is the main basic ion of the human erythrocyte and its concentration here is 20 times that of the blood serum. Hald and Eisenman[16] reported values ranging from 72 to 102 meq. per litre. Whole blood contains about half this amount. Muscle reportedly has 352 mgm. of potassium per 100 gm. of muscle tissue.[17] It is bound to protein in a ratio of 2.4 meq. for each gram of nitrogen.[14] Besides its association with protein it is probably bound to various hexose phosphates in the liver and muscle. Kamminga[18] working with isolated rat diaphragms found that their utilization of glucose was associated with a transfer of potassium but not inorganic phosphate into the muscle cells.

The body obtains its supply of potassium from ingested food and it has been estimated that the average daily intake is 75 to 100 meq. (3 to 4 gm.) per day.[1] The amount present in various foods and waters has been determined,[8, 9] but minimal daily requirements have not. Potassium is absorbed through the gastro-intestinal tract and equilibrium is maintained by excretion of a like amount in the urine and fæces. About 10 to 20% of the amount excreted appears in the fæces.[1, 10] The various digestive secretions have been analyzed for their potassium content. Saliva contains nearly 20 meq. per litre; œsophageal and gastric secretions 11 to 35 meq. per litre.[1, 11, 12] pancreatic juice approximately the same concentration as the serum,[1] and vomitus about five times that of the serum.[13] Most of this potassium is reabsorbed in the distal portions of the intestinal tract.

As will be shown later, renal function is of the utmost importance in relation to potassium equilibrium. In a healthy individual with normal renal function, 80 to 90% of the daily loss of potassium is accounted for by renal excretion. Tarail and Elkinton[14] studying normal subjects on isocaloric diets noted that when the diet was nearly potassium free, a daily loss of 49 to 50 meq. occurred. This indicated a failure of normal functioning kidneys to conserve this cation, when the potassium in the diet was low to absent. It was also found that when extra amounts were given, there was no retention of potassium unless a pre-existing deficit of this ion was present.

With reference to renal excretion, one might estimate on the basis of a serum potassium of 5 meq. per litre and a twenty-four hour glomerular filtration rate of 180 litres, that the glomeruli would filter 900 meq. of potassium each twenty-four hour period. This is far in excess of 75 to 100 meq., the average daily excretion for an adult. This would indicate then that reabsorption of potassium by the renal tubular cells takes place, possibly in association with phosphorylation during tubular reabsorption of glucose.

It has been stated that potassium is present in both the extra- and intra-cellular fluid compartments. The former, which comprises 20% of the body fluid, has a concentration of potassium approximating that of the blood serum. The normal blood serum values in man range from 3.6 to 6.2 meq. per litre according to Marinis *et al.*,[15] though most values are found between 4 and 5 meq. per litre. The total extra-

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cellular fluid potassium for a 70 kg. adult would be about 65 to 70 meq.

Rôle in carbohydrate metabolism.—Glucose is considered to be phosphorylated as it crosses the intestinal tissues on its way from the intestinal tract to the liver. It appears that potassium is essential for the process. Glucose is thought to be converted into a mono-potassium hexose diphosphate. Certainly the concentration of potassium increases in the liver with the movement of glucose into this organ. Fenn[19] has shown that glycogen cannot be deposited in the liver unless accompanied by appropriate quantities of water and potassium. Darrow[4] reported that glycogen is deposited with about 0.36 millimols of potassium per gram of glycogen during glycogenesis. Further, it is suggested by Fenn[1] that potassium follows the carbohydrate cycle from the liver to muscle and back again. Adrenalin causes a temporary elevation of venous blood sugar and serum potassium presumably by release of glucose from the liver. Generalized asphyxia of an animal by stimulating the adrenals likewise produces a rise of blood sugar and potassium.[1] Potassium and lactic acid rise together in the venous blood after exercise; their subsequent fall in the venous blood is associated with a concomitant rise in the liver.[1] A fall in both is noted in the serum following the injection of insulin. Gardner and associates[20] have reported that rats fed a potassium deficient diet for 40 to 60 days showed abnormally high liver and muscle glycogen concentrations, whereas those kept on the same diet 90 to 120 days showed almost absent liver and muscle glycogen. The latter group also had markedly elevated oral glucose tolerance curves.

Potassium furthers its importance in carbohydrate metabolism by being intimately linked with the metabolic processes of the adenylic acid system. This system supplies energy laden phosphate bonds for the formation of glycogen from glucose and it is also a means of conserving energy bonds released following the breakdown of glycogen. Boyer *et al.*[21] have given experimental evidence that potassium has a marked accelerating effect on the formation of adenosine triphosphate and pyruvate from phosphopyruvate and adenosine diphosphate. Adenosine triphosphate is well known for its rôle in the formation of glucose-6-phosphate from glucose, the first step in glycogen formation. These authors also found evidence that potassium was required for the production of creatine phosphate which serves as a storage form of excess high energy phosphate bonds.

Ionic relationships.—The regulatory mechanism that maintains a state of equilibrium allowing for a high intracellular and low extracellular potassium concentration is unknown. It is well known that disturbances in potassium metabolism follow disordered function of the adrenal cortex, and an upset in acid-base balance. In reference to acid-base balance one thinks of such electrolytes as sodium, potassium and chloride, and water; sodium is the main extracellular cation and potassium the chief intracellular cation. It is now well known that, even though these two cations have specific functions in the above locations, they do not as previously held, remain here, but are capable of transfer, in either direction across cell membranes. Such shifting is often the result of an excess or deficit in the concentrations of one cation in relation to the concentration of the other. It should be noted, however, that while sodium might replace potassium in the cell, it cannot substitute for the rôle potassium plays in normal tissue cell physiology. Furthermore, such transfer of ions depends on adequate water, and the maintenance of equilibrium on adequate cardiac and renal function.

Darrow[22] studying rats deficient in either sodium, potassium or chloride has been able to show that the concentration of serum bicarbonate varies directly with that of sodium and inversely with that of potassium. Rats on a diet low in potassium showed an increase in cellular sodium accompanied by a rise in serum bicarbonate and a depression of serum chloride. Prolonged water deprivation in dogs decreased the quantity of urine and, in turn, resulted in retention of sodium in preference to potassium which continued to be excreted at the expense of cellular protoplasm.[23] Vomiting due to high intestinal obstruction causes loss of chlorides, slight loss of sodium and potassium, a rise in serum bicarbonate and metabolic alkalosis associated with a low serum potassium.[24] A similar sequence of events follows prolonged gastrointestinal drainage.[25] From the above then, we understand that loss of chloride is compensated for by elevation of serum bicarbonate, and related to this is a retention of sodium with increased excretion of potassium as necessary to bring about electrolyte equilibrium. Metabolic alkalosis is the result. The infusion of excessive saline can produce the same picture.

Accompanying most of these states is a breakdown of muscle protoplasm with release of intracellular potassium which is excreted along with chloride in the urine. Continuation of this process, and the appearance of metabolic alkalosis, is associated with the entrance of sodium into tissue cells as deficit of potassium develops. Multiple disturbances in body electrolyte concentrations are more difficult to appraise, as serum bicarbonate in such cases no longer reflects the concentrations of sodium and potassium.[2, 4] In infantile diarrhœa loss of potassium is prominent, but sodium, which one would expect to be elevated in the cell is frequently low. The acidotic state in infantile diarrhœa then, may be accompanied by low values for both intracellular potassium and sodium, *i.e.*, there is a loss of relationship between serum bicarbonate and muscle composition.

Heart. — Ringer,[26] in performing frog heart studies, demonstrated the importance of having the proper amount of potassium in the medium, if the frog heart was to continue beating. If excess potassium is present the heart will stop in diastole and with low potassium the result is systolic standstill. Further knowledge of electrolyte influences on cardiac function came with electrocardiography, when abnormal complexes were recorded in uræmia[27] and in the recovery stage of diabetic coma.[28] The significance of these changes was at first not realized, and only in more recent years have they been correlated with hyperkalæmia and hypokalæmia. Harris *et al.*[29] were the first to correlate the electrocardiographic changes associated with elevated serum potassium levels; these followed the intravenous administration of potassium chloride in man. Winkler *et al.*[30] reported a regular sequence of electrocardiographic changes appearing concomitantly with increasing levels of serum potassium, following the intravenous administration of potassium chloride in dogs. These characteristic patterns of hyperkalæmia have now been reported in some cases of uræmia[31 to 37] and in a twelve-day-old infant that survived a serum potassium of 12.27 millimols per litre.[38] The electrocardiographic features of hypokalæmia are now familiar from studies made during recovery from diabetic acidosis and coma,[39 to 43] familial periodic paralysis,[44] in chronic nephritis with hypokalæmia,[45] following excessive vomiting,[24] and accompanying alkalosis in certain postoperative patients.[46, 47]

The electrocardiogram taken during hyperkalæmia reveals changes which appear dependent on the amount that the serum potassium has increased above normal. Wener and deLeeuw[37] in adults and Winkler, Hoff and Smith[30] in dogs, report the earliest change to be a disturbance in the T wave. Wener and deLeeuw[37] found an elevation of the T wave when the serum potassium level ranged from 6.0 to 7.4 meq. per litre. Depression of the S-T segment and diphasic or inverted T waves appeared when the potassium rose above 7.4 meq. per litre. P waves disappeared at serum levels above 8.5 meq. and complete disintegration of the QRS complex was recorded terminally when the serum potassium level was 8.9 meq. per litre. As well as the variations noted above, there may be disturbances in rhythm. Auricular standstill as noted by loss of the P waves, may be accompanied by bradycardia, idioventricular rhythm and delayed intraventricular conduction.

The patterns due to hypokalæmia are now accepted as quite specific and are utilized as a means for discovering low serum potassium values in patients not receiving quinidine or digitalis and where myocardial infarction is not suspected. The first variation from normal in the electrocardiogram involves the T wave which begins to broaden, become rounder and flatter. In about 50% of the cases there is depression of the S-T segment. This feature is not diagnostic, however, as S-T segment depression accompanies hyperkalæmia, and it has been found to be related to the degree of acidosis existing in diabetic acidosis.[40] The T wave may be inverted with depressions of the S-T segment. The QT interval may be prolonged to as much as 50% of the normal value. The P wave and P-R interval are usually normal, as is the QRS complex. Arrhythmias that may appear are sinus tachycardia, auricular extrasystoles, auricular flutter, ventricular extrasystoles and bigeminal rhythm. That these changes are the result of depleted myocardial potassium stores is suggested by the investigations of Orent-Keiles and his associates.[48, 49] Their rats kept on a very low potassium diet developed myocardial necrosis with scarring and the rats eventually died.

In agreement with this hypothesis Eliel and his colleagues[46] reported the finding of flattened T waves in two postoperative patients during alkalosis and hypochloræmia, but preceding a fall in the serum potassium. Somewhat similar circumstances are noted in the electrocardio-

grams of Fig. 1 in the review of Martin and Wertman.[40] The electrocardiogram taken six hours after admission of case 2 to hospital in diabetic acidosis shows a broad T_2 and prolongation of the QT interval. The serum potassium was 5.40 meq. per litre, but on admission had been 6.70 meq. per litre. Thus the electrocardiographic changes suggestive of hypokalæmia, were present in the presence of a normal serum value, but developed with a fall in the serum concentration. These are not common findings, however. During the early stages of recovery from diabetic coma the electrocardiogram is usually normal, with the serum potassium levels likewise, but the cellular potassium concentrations depressed.

It may be stated then, that the electrocardiogram is usually, but not always, a reliable means for revealing the presence of hypokalæmia. The relative importance of the serum potassium level is suggested when one realizes that the sudden administration of potassium chloride intravenously can precipitate such changes in cardiac rhythm as intraventricular block and ventricular fibrillation[50] with eventually cardiac arrest in diastole. Winkler *et al.*[30] stressed the influence of the serum level as the determining factor in the cardiac manifestations of potassium intoxication in dogs, and earlier Winkler *et al.*[51] had reported that large amounts of potassium chloride could be tolerated intravenously if given at a slow rate. Crismon and his associates[52] investigating the effect on the electrocardiogram of intraperitoneal injections of potassium chloride in cats, found that heart block was produced when the serum level for potassium ranged from 8.26 to 13.4 meq. per litre. The effective lower values were apparently associated with more rapid rates of administration.

One cannot stress then only the actual serum level or the intracellular concentration as the main factor in disturbing cardiac function, but must also acknowledge the importance of the rate of rise or fall of serum potassium (or the rate of entry of potassium into the cell). It was also found by Crimson and his associates, that during and after the injection of potassium chloride, the heart tissue took up more potassium than the skeletal muscle. Correlation of the electrocardiographic signs of potassium intoxication with amounts of electrolytes found in skeletal and cardiac muscle and in serum, failed to demonstrate a relationship between the amount of potassium found in the heart and the appearance of the signs of toxicity. The uptake of potassium was associated with loss of sodium and accumulation of chloride. It appears then, that cardiac abnormalities accompany abnormal concentrations of potassium in the serum, but that they are more striking with sudden changes in the concentration of potassium in the serum. This may occur because the sudden change in the serum level precipitates a redistribution of electrolytes within the myocardial cell, or it may be that the sudden change produces such an irregular relationship between the intracellular and extracellular electrolytes that normal cardiac function or intracardiac conduction is upset. In other words one cannot say that the electrocardiographic pattern of hypokalæmia is purely dependent on a low serum potassium value alone. The same conclusions pertain to the patterns related to hyperkalæmia.

Nervous system.—Nerve fibres are surrounded by a semipermeable membrane and when at rest in the presence of adequate oxygen, the electrical charge on the outside is positive and on the inside negative, *i.e.*, a potential difference exists across the membrane. Following stimulation, transmission of the impulse is considered dependent on electrical and chemical factors. Electrical excitation infers the presence of ions within the membrane, especially potassium ions. With stimulation the membrane becomes permeable and potassium ions readily diffuse out into the extracellular fluids. With rest there is loss of permeability and potassium is once more retained. In periods of potassium depletion, the membrane permits sodium to enter the cell.

Nachmansohn's contributions on nervous tissue conduction have recently been reviewed.[53, 54] He has stressed the importance of acetylcholine as the chemical agent important in impulse propagation by nerve fibres. Stimulation is stated to release acetylcholine esterase which in turn permits permeability of the membrane; then the esterase disposes of actylcholine permitting recovery of the initial potential. It has previously been shown that adenosine triphosphate formation is accelerated by the presence of potassium.[21] This is interesting because in the presence of adenosine triphosphate acetylcholine may be synthesized in nervous tissue.[54] Potassium has also been reported essential for the resynthesis of choline acetylase an enzyme required for the synthesis of acetylcholine.[1]

Adrenal gland.—Abnormal function of the adrenal cortex is associated with disturbances of

body electrolytes and acid-base balance. Adrenal insufficiency as seen in Addison's disease is accompanied by retention of potassium and loss of sodium and water. This abnormal situation can be reversed by the administration of desoxycorticosterone. Rats have developed hypopotassæmia following injections of desoxycorticosterone,[21] and its excessive use in Addison's disease has resulted in hypochloræmic alkalosis and hypopotassæmia.[55, 56] A derangement of electrolytes may also accompany hyperadrenocorticism of Cushing's syndrome[57, 58] and following administration of ACTH.[59, 60] Furthermore, major surgery by producing an alarm reaction, may produce such indications of increased adrenocortical function as a fall in circulating eosinophils,[61] and an increased excretion of urinary corticoids.[62] With this evidence Eliel and his associates[46] believe that the alarm reaction following surgical trauma, probably promotes renal loss of potassium with retention of sodium relative to chloride, and the development of metabolic alkalosis.

ETIOLOGY AND MECHANISMS OF PRODUCTION OF HYPOKALÆMIA AND HYPERKALÆMIA

Hypokalæmia. — Hypokalæmia has resulted from certain experimental procedures and has been recognized in many clinical conditions.

The mechanisms of production of hypokalæmia vary somewhat. Butler[63] found that testosterone therapy produced a fall in serum potassium. This was felt to be the result of nitrogen retention with deposition of tissue protein, the latter being accompanied by an increase in intracellular potassium. Desoxycorticosterone, ACTH and cortisone stimulate an increased tissue catabolism and increased urinary excretion of potassium. This results in decreased muscle and serum potassium accompanied by sodium retention.[22] Burns and tourniquet trauma damage tissue cells permitting release of intracellular potassium. This may be accompanied by elevation of serum potassium[65, 86] and an increase in intracellular potassium in uninjured cells.[65] The serum potassium concentration may be lowered with recovery from shock. This is dependent on re-establishment of adequate renal function and probably the stimulus of the alarm reaction. Starvation accompanied by adequate renal function, results in depletion of body potassium stores due to continuous renal elimination of potassium released during tissue catabolism.

Diabetic acidosis. — Hypokalæmia developing during diabetic acidosis or appearing during the treatment of diabetic coma is the result of numerous factors. First, impairment of carbohydrate metabolism leads to depletion of glycogen stores and release of tissue proteins. This in turn is accompanied by a release of intracellular potassium. Secondly, with nausea and vomiting there is some loss of potassium, but of more importance is the diminished intake of food (potassium). Thirdly, renal excretion of potassium continues. At the time therapy is instituted there is a tissue deficit of potassium while the serum concentration may be normal or even slightly elevated. Fourthly, insulin opens an avenue for serum potassium depletion by promoting a decrease in blood sugar and an increase in liver glycogen. The entrance of glucose into hepatic cells is accompanied by potassium and the serum level falls. Finally, fluid replacement, by improving renal function, permits potassium excretion, and it also expands the extracellular fluid compartment, diluting the concentration of electrolytes therein.

Holler[39] was the first to draw attention to the muscular weakness and flaccid paralysis appearing as a complication during recovery from diabetic coma. His patient's clinical picture was so like that seen during an attack of familial period paralysis that he immediately suspected the possibility of a potassium deficit. This was shown to be the case by serum potassium determination and electrocardiography. Since this report 10 similar cases have been reported[41, 43, 70, 87, 88] showing muscular disturbances. Of this number 4 females failed to recover. Nicholson and Branning[89] have records of 5 other cases that died 14 to 72 hours after admission, with symptoms suggestive of potassium deficiency.

The records of 181 coma admissions to the Montreal General Hospital were recently reviewed.[90] The group consisted of those cases treated since the institution of insulin therapy in 1922 up to the appearance of Holler's paper in 1946. The classification of coma as applied to this group, has appeared elsewhere.[91] Of this group four cases demonstrated clinical evidence of disturbed potassium balance. One case that developed a flaccid quadriplegia recovered. The other three died. One of the latter group developed marked muscular weakness and difficulty in respiration 10 hours after admission, for which the autopsy revealed no pathological basis. The other two cases that failed to recover

had flaccid paralysis and elevated blood ureas, 101 mgm. per 100 c.c. and 106 mgm. per 100 c.c. respectively. The case with a blood urea of 106 mgm. % however, had had an electrocardiogram during the period of paralysis, and flattening of the T waves as well as a prolonged QT interval were evident. On the basis of clinical evidence alone we concluded that disturbance of potassium metabolism was a prominent feature in 2.2% of the coma cases treated in the period designated and was possibly a cause of death in 1.6% of the cases. From this study and from the reports appearing in the literature concerning coma cases, one might suggest that clinical disturbances due to hypokalæmia are quite infrequent. This inference as will be considered later, is of course influenced by the therapeutic regimen employed. In contradistinction to this infrequency of clinical manifestations of hypokalæmia, is the actual frequency in which a depression of serum potassium occurs in cases of diabetic acidosis and coma. The majority of case studies reported reveal that well over 50% show a drop in the serum level as therapy proceeds.

One should not fail to realize that there are many electrolyte disturbances in diabetic coma other than those involving potassium. Great stress has been laid on the rôle of potassium in producing abnormalities of cardiac function. Martin and Wertman[40] have drawn attention (1) to the correlation existing between sagging ST segments and the lowered carbon dioxide combining power present during diabetic acidosis (2) to the correlation between prolonged QT intervals and the low ionized serum calcium and (3) the effects of anoxia and azotæmia.

Renal disease.—Since Smillie's[92] experiments in 1915, there has been great caution regarding the use of potassium salts in renal disease, because of the danger of potassium intoxication in the presence of impaired renal function. In 1944 Brown and his associates[45] published their observations and findings in two cases of chronic nephritis that had had recurrent episodes of flaccid paralysis. One case which showed electrocardiographic evidence of hypokalæmia, responded to oral potassium chloride. After receiving 8 gm. potassium chloride the patient's electrocardiogram reverted to normal. The other case on one occasion when flaccid paralysis was present, had a serum potassium of 2 meq. per litre. Both of these cases were relieved of their paralysis by ingestion of potassium chloride. Neither was considered to have had renal insufficiency, however, because of the absence of abnormal nitrogen retention. The authors speculated that the diseased kidneys were unable to form ammonia for acid radical excretion and as a result, base including potassium, was utilized. In 1949 Nicholson and Spaeth[45] reported another case of chronic nephritis that developed hypokalæmia.

Wener and deLeeuw[72] treated three cases of uræmia with an artificial kidney according to the method of Kolff. In two of the cases potassium chloride was not added to the dialyzing fluid. In one of these cases enough potassium was removed by artificial dialysis, to produce electrocardiographic evidence of hypopotassæmia; that such was present was verified by a serum potassium determination.

Infantile and other diarrhœas.—It was earlier stated that serum HCO_3 bears a close relationship to muscle composition,[93] *i.e.*, with depression of the serum HCO_3 one could expect to find low muscle sodium and high muscle potassium values. This relationship, however, is dependent on normal renal function. Severe infantile diarrhœa results in acidosis and dehydration, which upset renal function. With this disturbance in renal function the above serum HCO_3 muscle composition relationship is not maintained. Butler *et al.*, in their study of infantile diarrhœa[94] found potassium excretion to be in excess of nitrogen. It was concluded that unaffected tissue cells as well as those undergoing destruction served as a source for potassium. Further balance studies in 8 cases of severe infantile diarrhœa by Darrow and his colleagues[3] revealed the average retention of water and electrolytes to be H_2O—125 gm.; Cl—9.2 meq.; Na—9.5 meq. and K—10.4 meq. per kilogram of body weight. These values were interpreted as the average amount of water and electrolyte deficit present in each case on admission. The amounts of sodium and chloride lost were equivalent. The anticipated sodium loss should be about 25% in excess of chloride; from this it was concluded that the extra sodium not excreted had gone into the tissue cells. Here then, metabolic acidosis is accompanied by a low muscle potassium value with a muscle sodium concentration approaching normal. Rapaport[95] reporting on the post-acidotic state after rehydration of infants with diarrhœa, found after treatment with water and sodium bicarbonate, low serum values for calcium, phosphorus, potassium and phosphatases.

Other conditions resulting in frequent loose stools have been reported as causing hypokalæmia. Only three cases of sprue[43, 78] with potassium studies have been recorded in the literature. Two of them[78] were found to have serum levels as low as 1.1 meq. per litre. There were no potassium balance studies. One might speculate that, as with certain vitamins and such minerals as iron and calcium, potassium too was poorly absorbed from the gastro-intestinal tract. This might have been due to impaired fat and carbohydrate absorption. This inability to absorb, associated with continued renal loss of potassium would produce a negative potassium balance as with starvation.

In the case of cholera, it is quite probable that hypokalæmia might result. A report by Huang and Mao[79] is taken as the basis for such an occurrence. They treated 1,620 cases of Asiatic cholera, of which only 11, on recovery, developed pa-pin (transient paralysis). Pa-pin was previously considered to be the result of barium chloride poisoning and it was not alleviated by therapeutic use of potassium chloride. In the 11 cases of pa-pin which appeared following recovery from cholera, barium chloride as the causative agent was excluded. Because of the similarity of pa-pin to familial periodic paralysis a 2% solution of potassium chloride was tried intravenously and gave dramatic results. It was concluded that hypokalæmia must have existed. These conclusions could not be substantiated as the authors were unable to make serum potassium determinations.

Familial periodic paralysis.—The appearance of flaccid paralysis in association with hypokalæmia was originally demonstrated in familial periodic paralysis.[80, 82] Episodes of paralysis have been precipitated by the ingestion of a large meal, and carbohydrate,[80] and by the administration of insulin[81] and adrenalin.[82] In each instance the attack appeared to be the result of carbohydrate having been taken into tissue cells. It is of interest, however, that the attack is not associated with a disturbance in the blood sugar level nor with an abnormality of the glucose tolerance test.[96] Furthermore, the onset of hypokalæmia is not due to excessive renal elimination of potassium.[1, 97, 98] In fact, there may be decreased elimination.[99] Danowski and his colleagues[100] studying potassium shift from the extracellular compartment, found that even though there was a sharp decline in serum potassium with an attack of paralysis, there was only a small amount of potassium transferred to the intracellular phase. The presence of a serum potassium deficit in association with the onset of an attack is strongly suggested by the dramatic results which follow the therapeutic use of potassium chloride. One would speculate then that an intracellular deficit preceded the extracellular drop in potassium prior to an episode of paralysis. Darrow, reported by Danowski,[99] in one case found low muscle potassium, but the significance of this finding was marred by the atrophic muscle changes due to post-mortem. Howard[101] reports that muscle analyses have revealed normal concentrations for potassium.

Thus, the only conclusion possible so far, is that the appearance of most attacks is in association with a transfer of potassium from the extracellular compartment to the cells, which may already have a normal content for potassium. This transfer is usually but not always, accompanied by a fall in serum potassium. Gass, Cherkasky and Savitsky[6] and Ziegler[102] have made reference to a total of five cases in which a flaccid paralysis occurred in the presence of normal serum values for potassium. Also disturbing was Finch's[33] report of two cases showing flaccid quadruplegia when hyperpotassæmia existed. This would indicate then that the serum level in itself is not the main etiological factor of the paralysis. Danowski[100] feels that a disturbance in carbohydrate combustion in skeletal muscle, causes a transfer of potassium to these cells, liver cells not being involved. The latter are excluded because insulin and ephedrine, while precipitating an attack of paralysis, cause glycogenolysis with release of glucose and potassium from the liver. The glucose released from the liver is transferred to the muscle.

It is very difficult then to associate the manifestations of periodic paralysis with only a change in intracellular or extracellular concentrations of potassium. A disturbance in the distribution of potassium in the body is suggested, but the nature of the disturbance is unknown. We have already referred to the nature of potassium utilization, especially in relation to adenosine triphosphate which functions in neuromuscular transmission. It might be that the specific disturbance is an inability of the neuromuscular mechanism to function, due to an inherent defect, which (1) prevents ready utilization of available potassium; (2) requires the presence of a greater than normal concentration of potassium for normal function; (3) is associ-

ated with an insufficiency of some catalyst or enzyme which is required for use by muscle cells during rest or during storage of glycogen.

Postoperative hypokalæmia with hypochloræmia.—Postoperative hypokalæmia with hypochloræmia and metabolic alkalosis have recently been reviewed.[25, 46, 47, 64] These articles point out that a definite clinical picture has been recognized for years in postoperative patients who developed hypochloræmia, but only recently has the importance of an associated deficit of potassium been recognized. Randall *et al.*[25] in 1949 described three abdominal surgical cases in which vomiting and the use of Miller-Abbott drainage permitted constant removal of gastro-intestinal contents. It was found that 4 to 9 days postoperatively a clinical symptom complex developed, as well as hypochloræmia and alkalosis, in spite of an adequate intake of sodium chloride and water. It was recognized in this group of cases that restriction of food by mouth and the continual aspiration of gastric juices permitted loss of potassium, sodium and chloride from the body; the latter was considered to be attended to by the giving of saline parenterally. They also noted that loss of potassium continued with adequate renal function. These authors stressed the rôle of hypopotassæmia in the metabolic disturbance and in the clinical syndrome that developed.

In this same year Pearson and Eliel[64] reported studies on 15 postoperative cases. This group differed from the above however in that many of the cases had had no loss of gastro-intestinal fluids. Evidence was submitted to suggest that the metabolic upset was the result of adrenocortical hyperfunction. In a more recent review Eliel *et al.*[46] report a total 32 cases. In this group of cases manifesting hypopotassæmia and hypochloræmic alkalosis there was no death that could be attributed directly to a deficit of potassium. Nine of 16 cases showed low serum phosphorus accompanying low serum potassium. All patients had serum protein studies, and each case showed a fall postoperatively with seven showing levels below normal. The lowest serum potassium values appeared from 3 to 26 days postoperatively. With 28 cases it was between 6 and 18 days. Space determinations in one case showed an increase in extracellular sodium relative to chloride on the second postoperative day. On the fifteenth postoperative day in spite of a shrinkage in extracellular fluid volume, there was a much greater concentration of sodium, being much in excess of the chloride content. It was concluded that much of this excess sodium had migrated into the cells already deficient in potassium, for example erythrocytes[46, 103] and muscle.[104] An elevation of serum bicarbonate accompanied this excessive retention of sodium. Administration of potassium was followed by a diuresis of water and sodium, an elevation of serum protein and a retention of potassium in excess of nitrogen. Their conclusions regarding the pathogenesis of postoperative hypopotassæmia were similar to those of Randall except that in their cases loss of gastro-intestinal secretions was insignificant and greater stress was placed on the rôle of adrenocortical hyperfunction. A final factor that should not be overlooked is the use of testosterone in some postoperative patients to promote nitrogen retention.[63] Testosterone, however, while lowering serum potassium does not encourage loss of potassium from the body.

Hyperkalæmia.—Attention has already been directed to a case reported by Smillie[92] in which sudden collapse due to potassium intoxication appeared after oral administration of 10 gm. of potassium chloride. Another case of potassium intoxication has been referred to in which an infant received intravenous potassium chloride.[38] In these two cases potassium appeared in the serum at a rate exceeding that at which it could be removed. Excessive intake then is one means of producing hyperkalæmia. It was difficult to produce hyperkalæmia in dogs with normal functioning kidneys by excessive intake of potassium chloride, though it was readily achieved if the ureters were tied.[105] Most of the cases that have been reported showing electrocardiographic indications of hyperkalæmia have been those in which renal insufficiency, or uræmia, were present.[27, 29, 31, 37] Two factors appear responsible for the accumulation of potassium in the serum: (1) tissue breakdown with release of potassium into the extracellular spaces and (2) concomitant oliguria or anuria. Renal disease without suppression of urine volume is unlikely to cause hyperkalæmia.[105] It should also be remembered that many cases with uræmia fail to demonstrate signs of potassium toxicity,[36, 106] as adequate facilities for renal excretion of potassium persist. Leaf and his associates[107] have investigated the mechanism whereby adequate potassium elimination continues in renal insufficiency. Previously Elkinton *et al.*[108] had shown that renal tubular reabsorption prevented all the

potassium appearing in the glomerular filtrate from being lost in the urine. From their observations they also felt that hyperpotassæmia in renal insufficiency was due to depression of the glomerular filtration rate. They have recorded such low rates as 5 litres compared to 180 litres for a 24-hour period. Leaf *et al.* in their investigations used creatinine clearance times the serum potassium concentration as a measure of glomerular filtration of potassium. A ratio of excreted potassium to filtered potassium greater than 1.0 indicated that more potassium was cleared by the kidney than could be accounted for by glomerular filtration. In four patients with renal insufficiency the ratio varied from 1.21 to 1.64; thus in these four patients renal tubular clearance of potassium must have occurred. This then, is probably the reason why most patients with renal insufficiency, *i.e.*, with a decreased glomerular filtrate, are able to maintain normal serum potassium levels.

SIGNS AND SYMPTOMS

Hypokalæmia. — The signs and symptoms of familial periodic paralysis were well known before the etiological factor was ascertained. The attack often appeared during sleep, having followed ingestion of a heavy meal. On being discovered in the morning, the patient though alert and conscious, was found otherwise to be completely helpless with a flaccid paralysis involving all extremities. This degree of involvement, however, is not always noted. There may be only muscular weakness and loss of muscle tone, or one or more of the extremities may show complete flaccid paralysis. An ascending paralysis of the type of Landry has been described with involvement of the lower extremities preceding that of the upper extremities, with finally, the trunk being involved. The final picture may be that of complete flaccid paralysis from the neck down, with the individual unable to move his head. Also, one may see marked respiratory difficulty associated with depression of activity of the intercostal muscles and diaphragm. The head may be thrown back, and with the use of the accessory muscles of respiration, a peculiar fish-mouth type of respiration may be produced which is rapid, shallow and gasping in character. Consciousness and the cranial nerves usually remain undisturbed, though difficulty in swallowing is not infrequent. Ptosis and blurring of vision have been reported. Reflexes may be absent, as well as the reaction to Faradic stimulation. Sphincter function is most often unaffected.

Cardiac findings described are transient dilation, at times associated with a systolic murmur over the precordium; tachycardia and hypertension.

The attack usually lasts 8 to 48 hours without treatment. This familial disease may be inherited as either a recessive or dominant trait and affects males three times as often as it does females.[96]

In infantile diarrhœa the signs are often masked by those of severe dehydration, acidosis, malnutrition and shock. With treatment a fall in serum potassium may result in loss of muscular tone, paralytic ileus and abdominal distension. Lethargy or irritability, followed by convulsions, as well as difficulty in respiration and disturbance of cardiac function, are also part of this clinical complex. Generalized œdema may appear and also the carpopedal and laryngeal spasms of hypocalcæmic tetany. Intracranial and gastrointestinal hæmorrhages are complicating features.

The hypokalæmia of diabetic coma may also be accompanied by certain non-specific as well as specific clinical features. The non-specific signs and symptoms are muscular weakness, anorexia, intestinal distension, paræsthesias of the limbs, and lethargy. The skin may be warm and red. Cardiovascular signs of involvement which have been recorded are increased areas of cardiac dullness, possibly a systolic precordial murmur, increased pulse pressure, and tachycardia.

Specific signs of potassium deficiency are similar to those of the other conditions mentioned, *i.e.*, muscular weakness and respiratory embarrassment, flaccid paralysis involving one or more extremities, and characteristic electrocardiographic patterns.

The time of appearance of hypokalæmia in diabetic coma as well as the clinical manifestations is somewhat variable. Martin and Wertman[40] in their series of cases, found a fall in serum potassium to come between 12 and 24 hours after instituting treatment, whereas Nadler *et al.*[109] found that serum values begin to fall as early as 2 hours and as late as 18 hours. Holler's case began to show respiratory distress 12½ hours after admission to the hospital. Nicholson and Branning's two cases showed signs 9 and 24 hours after admission. It appears then that the serum level for potassium may begin to fall in a period of 2 to 3 hours and the clinical picture of potassium deficiency may appear as early as

6 to 8 hours, after starting treatment. It is more likely, however, that the signs and symptoms will appear 12 to 24 hours after initiation of treatment of diabetic coma and may last throughout a period of 24 hours in spite of the giving of liberal amounts of potassium.[87]

It has been noted above that surgical procedures, more specifically major abdominal surgery, can produce a well recognized clinical syndrome associated with hypokalæmia, hypochloræmia and metabolic alkalosis. In Randall's series[25] in which gastric suction was a factor the symptoms appeared 4 to 9 days postoperatively. In the series of Eliel *et al.*[46] depression of serum potassium was recorded anywhere from the third to the twenty-sixth postoperative day. The latter group of authors found abdominal distension and cramps, lethargy, apathy and depression, muscular weakness, nausea and vomiting, and anorexia to be the most frequent of signs and symptoms. Others were dependent œdema, paralytic ileus; nervousness, irritability and apprehension; irregularity of pulse; confusion, disorientation; tetany, and in one patient only, shallow respiration. The usual electrocardiographic manifestations have also been described.

Hyperkalæmia.—The signs and symptoms here are chiefly those of neuromuscular and cardiac disturbances sometimes in association with those of shock. The patient may show a cold gray pallor, peripheral vascular collapse, poor heart sounds and low blood pressure. The pulse may be a very slow rate and quite irregular. The electrocardiographic features have been given. The patient may also appear listless and confused or complain of paræsthesias of the hands and feet. Finch and his associates[33] also found potassium intoxication to produce loss of position and vibration senses and deep reflexes. Shallow, laboured respirations, weakness of facial muscles and flaccid quadriplegia may appear in association with hyperkalæmia, though apparently much less frequently than with hypokalæmia.

THERAPEUTIC USE OF POTASSIUM

Potassium replacement measures are now required for the prevention as well as the treatment of the hypokalæmic state. Preventive measures require first a knowledge of the causes of potassium deficit; second, the elimination or modification of any specific measure used in the treatment of the major illness which might encourage the development of hypokalæmia, and finally the prophylactic use of potassium salts. These considerations will be dwelt with in the conditions to follow.

Diabetic acidosis and coma.—The sudden appearance of such acute symptoms as respiratory embarrassment, flaccid paralysis or cardiac distress are indications for emergency measures such as the use of intravenous potassium salts. Potassium chloride of 0.5 to 2.0% strength is frequently utilized. One must allow at least 20 to 30 minutes for the intravenous injection of 1.5 gm. of the salt, *i.e.* 20 meq. of potassium. This amount may be repeatedly given if clinical signs and electrocardiographic indications are evident. The greatest amount administered, to be reported, is 33 gm. given intravenously over a period of 18 hours.[87] Usually 1.5 to 4.5 gm. are adequate. Following relief of the acute symptoms one should provide oral doses of 0.5 gm. every half hour for four to six doses or 1.0 gm. hourly for three to four doses. Oral administration is a much more welcome route as overdosage is prevented by decreased absorption or vomiting, or the uniform rate of absorption may be balanced by renal elimination.

Wilson and Ellis[110] suggested the use of potassium dihydrogen phosphate intravenously rather than potassium chloride, because they found it to be more readily taken up by tissue cells. Sinden *et al.*[111] recommended the use of a mixture of potassium phosphate 2.0 gm., and potassium dihydrogen phosphate 0.4 gm. in water. Another recommended solution is that of Elkinton and Tarail[112] who use potassium monohydrogen phosphate and potassium dihydrogen phosphate in a molar ratio of 3.55 to 1.0 (4.5 gm. to 1.0) to yield a pH of 7.35.

Certain precautionary measures are indicated if one is to prevent a precipitous fall of the serum potassium level. As has been noted, patients in severe diabetic acidosis have had a decrease in body potassium stores and institution of treatment may cause a depression of serum potassium. Treatment of diabetic acidosis and coma require insulin and rehydration. The latter is usually accomplished by the use of parenteral saline. Some, however, advocate the early use of glucose intravenously for rapid restoration of liver glycogen. This is not good practice if one wants to prevent escape of potassium from the serum. One must guard against such use until the blood sugar is near normal, and by then, oral intake of carbohydrate is usually well under way. By this method sudden

withdrawal of potassium from the serum is prevented, and as the oral carbohydrate is ingested for replenishment of glycogen stores it is accompanied by the potassium present in such fluids as orange juice. To strengthen this hypothesis one has only to recall that the cases reported in the literature[39, 41, 71, 87, 88] as having developed flaccid paralysis and respiratory difficulty in association with hypokalæmia, were cases that received intravenous glucose.

One might argue against the excessive use of saline, especially if a deficiency of potassium exists. Of course saline should not be used for treatment when hypokalæmia is present, but in the routine treatment of diabetic coma saline is freely and nearly always profitably used, in quantities of 3 to 6 or more litres. Root and Riseman[113] reported one case which received 12,000 ml. in 11 hours, 4,000 ml. of this amount being subcutaneously. This patient apparently did not develop any of the signs of serum potassium deficiency, but this was probably due to a concomitant period of anuria and oliguria. At the Montreal General Hospital 1 to 3 litres of normal saline are first given and then when renal function appears to be satisfactory further intravenous therapy consists of Ringer's solution, 1 to 3 litres as required. This solution is prepared at the hospital and each litre contains potassium chloride 0.3 gm., sodium chloride 7.0 gm., and calcium chloride 0.25 gm. Other institutions utilize multiple electrolyte solutions for parenteral therapy.[114] Biochemically it is probably proper to employ such solutions because other electrolytes than sodium, potassium and chloride are disturbed, notably phosphate.

These solutions are most valuable if, because of unconsciousness, oral intake is impossible for a period of many hours. In such cases parenteral administration of glucose will become necessary and this is best accomplished by using a solution containing besides glucose, such electrolytes as sodium, potassium, magnesium, chloride and phosphorus, and vitamins. Potassium salts should not be permitted parenterally until one is certain renal function has been re-established and such stock solutions employed should have a distinctive colour. Usually by the time renal function is definitely evaluated, oral intake of broth, orange juice or gruel has begun and one then has both a safer and more natural path for restoring depleted potassium and other electrolyte stores. At the Montreal General Hospital 200 ml. of orange juice are given every hour on the hour, beginning 5 to 6 hours after starting treatment. Fat free broth salted to taste is started at any earlier hour if possible, and is given every hour on the half hour. Each feeding of orange juice supplies approximately 8 meq. of potassium and each feeding of broth 4 meq.[115] In the five-hour period following institution of oral feedings of orange juice and broth the patient will have received 60 meq. of potassium which is equivalent to 4 gm. of potassium chloride. One can usually expect to have satisfactory results with the proper use of insulin, normal saline and/or Ringer's solution especially if early use of oral fluids is possible.

Familial periodic paralysis.—Unless the patient is unconscious, prompt recovery from an attack follows the oral administration of 2 to 10 gm. of potassium chloride[96] or potassium citrate.[116] Inability on the part of the patient to take oral therapy would of course necessitate intravenous injections. In such instances 1 gm. of a 2% solution of potassium chloride over a period of 20 minutes should be given. To decrease the frequency of attacks, the prophylactic use of potassium chloride 0.3 gm. once to three times daily, abstinence from heavy meals especially before retiring, and moderate exercise are helpful.

Infantile diarrhœa.—At the time these cases are first seen measures are required to combat shock and the associated circulatory and renal failure. As long as oliguria is present normal saline, sodium lactate and glucose solutions are utilized. As renal function improves solutions with added potassium must be used. Darrow[4, 75] recommends 80 ml. per kilogram of body weight of a solution containing 122 meq. of sodium, 100 meq. of chloride, 35 meq. of potassium and 52 meq. of lactate per litre. This solution is formed by using 4.0 gm. of sodium chloride, 2.7 gm. of potassium chloride and 52 ml. of molar sodium lactate with the addition of water to make a litre. This solution may be used subcutaneously, but must be diluted one part to two parts of 5% glucose for intravenous use. Butler, and Talbot[117] use a similar solution which also contains phosphate. The ingredients per litre of 5 to 10% glucose are; sodium 30 meq., chloride 22 meq., potassium 15 meq., and phosphate 3 meq.

Darrow[4] cautions against the use of a solution containing over 20 meq. of potassium per litre. He also states that 100 to 150 ml. of fluid are required for every 100 calories metabolized, and at times glucose and water are all that are re-

quired as only water has been lost. Excessive use of saline initially will encourage the development of acidosis with high intracellular sodium. Rapoport[95] has stated that one must guard against the appearance of hypocalcæmic tetany with the re-establishment of adequate serum potassium concentration.

Postoperative hypokalæmia.—Randall and his co-workers[25] improved the potassium balance in surgical cases by giving preoperatively and postoperatively, 2 gm. of potassium chloride daily. Such measures are capable of reducing the incidence of weakness, listlessness, abdominal distension, cramps and nausea. Eliel and his associates[16] administer 50 meq. of potassium parenterally each day for such less traumatic procedures as herniorrhaphies. For such procedures as gastrectomies, where the daily losses of potassium in proportion to nitrogen are much greater, 80 to 100 meq. of potassium are provided each day. Potassium chloride 1.0 gm. every four hours supplies this amount of potassium.

The acute symptoms of hypokalæmia can be treated by the intravenous administration of 1.5 gm. of a 2% solution of potassium chloride which may be added to a litre of normal saline or glucose. Randall uses a solution containing sodium 110 meq., potassium 30 meq., chloride 140 meq. per litre of water. This solution may be given daily as a precautionary measure, but should not be started until the second day, or until one is sure of adequate renal function.

ACTH and cortisone.—These agents stimulate renal elimination of potassium. Hypokalæmia may be prevented and the incidence of glycosuria greatly diminished by the provision 0.9 gm. of potassium chloride three times daily, while the use of ACTH and cortisone continues.

TREATMENT OF HYPERKALÆMIA

The earlier methods investigated for the relief of potassium intoxication were those involving electrolytes antagonistic to potassium and certain measures found to produce hypokalæmia. Thus calcium gluconate intravenously has resulted in both improvement of clinical symptoms[31, 33] and the electrocardiographic signs of intoxication.[31, 33 118] Calcium chloride was of some benefit in another case suspected of bilateral renal cortical necrosis.[119] Besides using calcium, Finch *et al.*[33] injected 3% sodium chloride in one case. After having received 410 ml. the patient, having been moribund, was remarkably improved. This improvement lasted two hours when his condition once again worsened. One might expect that such a case having acidosis and hyperkalæmia would benefit from sodium. However, with depression of renal function the effects are only transient as the sodium accumulates within the tissue cells. Hypertonic saline has been beneficial in one case reported by Merrill *et al.*[119] in which a sodium deficit existed.

Of the measures which may lower the blood potassium, three are to be considered. First, testosterone, as has been mentioned encourages potassium and nitrogen return to, and retention within, tissue cells.[63] Testosterone propionate has not been a successful therapeutic tool; however, Merrill and his associates[119] recommend its use in anuric subjects for a period of 4 to 5 days to encourage potassium and nitrogen retention within the cell. Second, ACTH and cortisone are indicated if renal function is preserved. They are not recommended in the anuric case because of their nitrogen accumulating effects. Finally a most beneficial of therapeutic agent has been the combined use of insulin and glucose.[37, 120] By increasing the amount of stored glycogen both within the liver and muscle cell, insulin and glucose cause potassium to be removed from the serum.

More recent methods of removing body potassium are perfusion of the large bowel,[43] the artificial kidney,[37, 72, 74] and cation exchange resins. The first-named method is used but infrequently. In competent hands the artificial kidney is now quite successfully employed. Its success is dependent on the concentration of potassium in the dialyzing fluid being less than that of the serum. The effectiveness of this instrument is more definite and lasting and its use should not be that of a last chance venture. For further information on the artificial kidney one is referred to such authoritative sources as Kolff,[121] the originator of the dialyzing type of artificial kidney, the Montreal,[72, 122] and the Boston[73, 74] groups.

Cation exchange resins are a valuable means of removing sodium and now it appears also potassium[123, 124] from the intestinal tract. Their sulfonic and carboxylic side chains are capable of attracting such cations as sodium and potassium in exchange for hydrogen and ammonium. Elkinton and his associates[125] recently reported on their use in three patients with renal insufficiency and markedly diminished urinary output. They used an ammonium form of resin which contained no potassium. The resin was admin-

istered both orally and rectally. Both routes were effective for removing potassium, mainly from the extracellular fluid compartment. The results of the enemata of resins were more variable, but this mode was quite advantageous in those subjects where oral administration produced upper intestinal tract irritation. Gastric irritations as well as excessive withdrawal of sodium are apparently the major objections to the use of resins orally.

REFERENCES

1. FENN, W. O.: *Physiol. Rev.*, **20**: 377, 1940.
2. DARROW, D. C.: *Bull. New York Acad. Med.*, **24**: 147, 1948.
3. DARROW, D. C., PRATT, E. L., FLETT, J. JR., GAMBLE, A. H. AND WIESE, H. F.: *Pediatrics*, **3**: 129, 1949.
4. DARROW, D. C.: *New England J. Med.*, **242**: 978, 1014, 1950.
5. BODANSKY, O.: *Am. J. M. Sc.*, **218**: 567, 1949.
6. GASS, H., CHERKASKY, M. AND SAVITSKY, N.: *Medicine*, **27**: 105, 1948.
7. DARROW, D. C. AND PRATT, E. L.: *J. A. M. A.*, **143**: 365, 432, 1950.
8. MCCANCE, R. A. AND WIDDOWSON, E. M.: The Chemical Composition of Foods, 2nd rev. ed., Brooklyn Chem. Publishing Co., 1947.
9. BILLS, C. E., MCDONALD, W. N. AND SCHWARTS, M. C.: *J. Am. Dietic. A.*, **25**: 304, 1949.
10. BASSETT, S. H., ELDEN, C. A. AND MCCANN, W. S.: *J. Nutrition*, **5**: 1, 1932.
11. HOWARD, J. E. AND CAREY, R. A.: *Tr. Am. Clin. & Climatol. A.*, **60**: 1, 1948.
12. AUSTIN, J. H. AND GAMMON, G. D.: *J. Clin. Investigation*, **10**: 287, 1931.
13. FALCONER, M. A., OSTERBERG, A. E. AND BARGEN, J. A.: *Proc. Staff Meet., Mayo Clin.*, **14**: 22, 1939.
14. TARAIL, R. AND ELKINTON, J. R.: *J. Clin. Investigation*, **28**: 99, 1949.
15. MARINIS, T. P., MUIRHEAD, E. E., JONES, F. AND HILL, J. M.: *J. Lab. & Clin. Med.*, **32**: 1208, 1947.
16. HALD, P. M. AND EISENMAN, A. J.: *J. Biol. Chem.*, **118**: 275, 1937.
17. MYERS, V. C. AND MANGUN, G. H.: *J. Biol. Chem.*, **132**: 701, 1940.
18. KAMMINGA, C. E., WILLEBRANDS, A. F., GROEN, J. AND BLICKMAN, J. R.: *Science*, **111**: 30, 1950.
19. FENN, W. O.: *J. Biol. Chem.*, **128**: 297, 1939.
20. GARDNER, L. I., TALBOT, N. B., COOK, C. D., BERMAN, H. AND CONCEPCION, U. R.: *J. Lab. & Clin. Med.*, **35**: 592, 1950.
21. BOYER, P. D., LARDY, H. A. AND PHILLIPS, P. H.: *J. Biol. Chem.*, **149**: 529, 1943.
22. DARROW, D. C., SCHWARTZ, R., IANUCCI, J. F. AND COVILLE, F.: *J. Clin. Investigation*, **27**: 198, 1948.
23. ELKINTON, J. R. AND TAFFEL, M.: *J. Clin. Investigation*, **21**: 787, 1942.
24. BELLET, S., NADLER, C. S., GAZES, P. C. AND LANNING, M.: *Am. J. Med.*, **6**: 712, 1949.
25. RANDALL, H. T., HABIF, D. V., LOCKWOOD, J. S. AND WERNER, S. C.: *Surgery*, **26**: 341, 1949.
26. RINGER, S. AND MURRELL, W.: *J. Physiol.*, **1**: 72, 1878.
27. WOOD, J. E. JR. AND WHITE, P. D.: *Am. J. M. Sc.*, **169**: 76, 1925.
28. BELLET, S. AND DYER, W. W.: *Am. Heart J.*, **13**: 72, 1937.
29. HARRIS, I. AND LEVIN, D. A.: *J. Physiol.*, **89**: 153, 1937.
30. WINKLER, A. W., HOFF, H. E. AND SMITH, P. K.: *Am. J. Physiol.*, **124**: 478, 1938.
31. MARCHAND, J. F. AND FINCH, C. A.: *Arch. Int. Med.*, **73**: 384, 1944.
32. KEITH, N. M., BURCHELL, H. B. AND BAGENSTOSS, A. H.: *Am. Heart J.*, **27**: 817, 1944.
33. FINCH, C. A., SAWYER, C. G. AND FLYNN, J. M.: *Am. J. Med.*, **1**: 337, 1946.
34. TARAIL, R.: *Am. Heart J.*, **35**: 665, 1948.
35. STEWART, H. J., SHEPARD, E. M. AND HORGER, E. L.: *Am. J. Med.*, **5**: 821, 1948.
36. KEITH, K. M. AND BURCHELL, H. B.: *Am. J. M. Sc.*, **217**: 1, 1949.
37. WENER, J. AND DELEEUW, N. K. M.: *Canad. M. A. J.*, **61**: 406, 1949.
38. GOVAN, C. D. AND WEISETH, W. M.: *J. Pediat.*, **28**: 550, 1946.
39. HOLLER, J.: *J. A. M. A.*, **131**: 1186, 1946.
40. MARTIN, H. E. AND WERTMAN, M.: *Am. Heart J.*, **34**: 646, 1947.
41. FRENKEL, M., GOVAN, J. AND WILLEBRANDS, A. F.: *Arch. Int. Med.*, **80**: 728, 1947.
42. NADLER, C. S., BELLET, S. AND LANNING, M.: *Am. J. Med.*, **5**: 838, 1948.
43. NICHOLSON, W. M. AND SPAETH, W.: *South. M. J.*, **42**: 77, 1949.
44. STEWART, H. J., SMITH, J. J. AND MILHORAT, A. T.: *Am. J. M. Sc.*, **199**: 789, 1940.
45. BROWN, M. R., CURRENS, J. H. AND MARCHAND, J. F.: *J. A. M. A.*, **124**: 545, 1944.
46. ELIEL, L. P., PEARSON, O. H. AND RAWSON, R. W.: *New England J. Med.*, **243**: 471, 1950.
47. NELSON, R. M., FRIESEN, S. R. AND KREMEN, A. J.: *Surgery*, **27**: 26, 1950.
48. ORENT-KEILES, E. AND MCCOLLUM, E. V.: *J. Biol. Chem.*, **140**: 337, 1941.
49. FOLLIS, R. H. JR., ORENT-KEILES, E. AND MCCOLLUM, E. V.: *Am. J. Path.*, **18**: 29, 1942.
50. NAHUM, L. H. AND HOFF, H. E.: *J. Pharmacol. & Exper. Therap.*, **65**: 322, 1939.
51. WINKLER, A. W. AND SMITH, P. K.: *J. Biol. Chem.*, **124**: 589, 1938.
52. CRISMON, J. M., CRISMON, C. S., CALABRESI, M. AND DARROW, D. C.: *Am. J. Physiol.*, **139**: 667, 1943.
53. ECCLES, J. C.: *Am. Rev. Physiol.*, **10**: 93, 1948.
54. BISHOP, G. H.: *Ann. Rev. Physiol.*, **8**: 355, 1946.
55. THORN, G. W. AND FIROR, W. M.: *J. A. M. A.*, **114**: 2517, 1940.
56. TALBOT, J. H. AND SCHWAB, R. S.: *New England J. Med.*, **222**: 585, 1940.
57. MCQUARRIE, I., JOHNSON, R. M. AND ZIEGLER, M. R.: *Endocrinology*, **21**: 762, 1937.
58. KEPLER, E. J., SPRAGUE, R. G., MASON, H. L. AND POWER, M. H.: *Recent Prog. Hormone Research*, **2**: 345, 1948.
59. PEARSON, O. H., ELIEL, L. P., DOBRINER, K., RAWSON, R. W. AND RHOADES, C. P.: *Cancer*, **2**: 943, 1945.
60. SPRAGUE, R. G., POWER, M. H., MASON, H. L., ALBERT, A., MATHIESON, D. R., HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H. AND POLLEY, H. F.: *Arch. Int. Med.*, **35**: 199, 1950.
61. ROCHE, M., THORN, G. W. AND HILLS, A. G.: *New England J. Med.*, **242**: 307, 1950.
62. VENNING, E. H., HOFFMAN, M. M. AND BROWNE, J. S. L.: *Endocrinology*, **35**: 49, 1944.
63. BUTLER, A. M., TALBOT, N. B. AND MACLACHLAN, E. A.: *Proc. Soc. Exper. Biol. & Med.*, **51**: 378, 1942.
64. PEARSON, O. H. AND ELIEL, L. P.: *J. Clin. Investigation*, **28**: 803, 1949.
65. FOX, C. L., JR. AND BAER, H.: *Am. J. Physiol.*, **151**: 155, 1947.
66. BENEDICT, F. G.: A Study of Prolonged Fasting. Publication No. 203, Carnegie Institute of Washington, 1915.
67. HARROP, G. A., JR. AND BENEDICT, E. M.: *Proc. Soc. Exper. Biol. & Med.*, **20**: 430, 1922-23.
68. *Idem*: *J. Biol. Chem.*, **59**: 683, 1924.
69. ATCHLEY, D. W., LOEB, R. F., RICHARDS, D. W. JR., BENEDICT, E. M. AND DRISCOLL, M. E.: *J. Clin. Investigation*, **12**: 297, 1933.
70. NICHOLSON, W. M. AND SPAETH, W.: *Am. Clin. & Climatol. A.*, **59**: 246, 1947.
71. TUYNMAN, P. E. AND WILHELM, S. K.: *Ann. Int. Med.*, **29**: 356, 1948.
72. WENER, J. AND DELEEUW, N. K. M.: *Proc. Soc. Exper. Biol. & Med.*, **71**: 18, 1949.
73. MERRILL, J. P., THORN, G. W., WALTER, C. W., CALLAHAN, E. J. III AND SMITH, L. H. JR.: *J. Clin. Investigation* **29**: 412, 1950.
74. MERRILL, J. P., SMITH, S. III, CALLAHAN, E. J. III AND THORN, G. W.: *J. Clin. Investigation*, **29**: 425, 1950.
75. DARROW, D. C.: *J. Pediat.*, **28**: 515, 1946.
76. GOVAN, C. D., JR. AND DARROW, D. C.: *J. Pediat.* **28**: 541, 1946.
77. DARROW, D. C.: *J. Pediat.*, **26**: 519, 1945.
78. HARRISON, H. E., TOMPSETT, R. R. AND BARR, D. P.: *Proc. Soc. Exper. Biol. & Med.*, **54**: 314, 1943.
79. HUANG, K. W. AND MAO, Y. C.: *Am. J. M. Sc.*, **214**: 153, 1947.
80. BIEMOND, A. AND DANIELS, A. P.: *Brain*, **57**: 91, 1934.
81. AITKEN, R. S., ABBOTT, E. N., CASTLEDON, L. I. M. AND WALKER, M.: *Clin. Sc.*, **3**: 47, 1937.
82. ABBOTT, E. N. AND MCARDLE, B.: *Clin. Sc.*, **3**: 229, 1938.
83. BERRY, R. E. L., JOB, V. AND CAMPBLL, K. N.: *Arch. Surg.*, **57**: 470, 1948.
84. COOPER, D. R., JOB, V. AND COLLER, F. A.: *Ann. Surg.*, **129**: 1, 1949.
85. STEWART, J. D. AND ROURKE, G. M.: *J. Clin. Investigation*, **21**: 197, 1942.
86. MANERY, J. F. AND SOLANDT, D. Y.: *Am. J. Physiol.*, **138**: 499, 1943.
87. STEPHENS, F. I.: *Ann. Int. Med.*, **30**: 1272, 1949.
88. LOGSTON, C. S. AND MCGAVACK, T. H.: *J. Clin. Endocrinol.*, **8**: 658, 1948.
89. NICHOLSON, W. M. AND BRANNING, W. S.: *J. A. M. A.*, **134**: 1292, 1947.
90. STEPHENS, J. W.: Unpublished data.
91. RABINOWITCH, I. M., FOWLER, A. F. AND BENSLEY, E. H.: *Ann. Int. Med.*, **12**: 1403, 1939.
92. SMILLIE, W. G.: *Arch. Int. Med.*, **16**: 330, 1915.
93. MILLER, H. C. AND DARROW, D. C.: *Am. J. Physiol.*, **130**: 747, 1940.
94. BUTLER, A. M., MCKHANN, C. F. AND GAMBLE, J. L.: *J. Pediat.*, **3**: 84, 1933.
95. RAPOPORT, S., DODD, K., CLARK, M. AND SYLLM, I.: *Am. J. Dis. Child.*, **73**: 391, 1947.
96. TALBOT, J. H.: *Medicine*, **20**: 85, 1941.
97. PUDENZ, R. H., MCINTOSH, J. F. AND MCEACHRAN, D.: *J. A. M. A.*, **111**: 2253, 1938.
98. GAMMON, G. D., AUSTIN, J. H., BLITHE, M. D. AND REID, C. G.: *Am. J. M. Sc.*, **197**: 326, 1939.
99. DANOWSKI, T. S.: *Am. J. Med.*, **7**: 525, 1949.
100. DANOWSKI, T. S., ELKINTON, J. R., BURROWS, B. A. AND WINKLER, A. W.: *J. Clin. Investigation*, **27**: 65, 1948.

101. HOWARD, J. E.: *Connecticut M. J.*, **14**: 596, 1950.
102. ZIEGLER, D. K.: *Arch. Int. Med.*, **84**: 419, 1949.
103. KENNEDY, T. J. JR., WINKLEY, J. H. AND DUNNING, M. F.: *Am. J. Med.*, **6**: 790, 1949.
104. MUDGE, G. H. AND VISLOCKY, K.: *J. Clin. Investigation*, **28**: 482, 1949.
105. WINKLER, A. W., HOFF, H. E. AND SMITH, P. K.: *J. Clin. Investigation*, **20**: 119, 1941.
106. HOFFMAN, W. S.: *J. A. M. A.*, **144**: 1157, 1950.
107. LEAF, A., CAMARA, A. A. AND ALBERTSON, B.: *J. Clin. Investigation*, **28**: 1526, 1949.
108. ELKINTON, J. R., TARAIL, R. AND PETERS, J. P.: *J. Clin. Investigation*, **28**: 378, 1949.
109. NADLER, C. S., BELLET, S., REINHOLD, J. G. AND LANNING, M.: *Am. J. M. Sc.*, **218**: 308, 1949.
110. WILSON, H. E. C.: *Arch. Dis. Childhood*, **23**: 176, 1948.
111. SINDEN, R. H., TULLIS, J. L. AND ROOT, H. F.: *New England J. Med.*, **240**: 502, 1949.
112. ELKINTON, J. R. AND TARAIL, R.: *Am. J. Med.*, **9**: 200, 1950.
113. ROOT, H. F. AND RISEMAN, J. E. F.: *J. A. M. A.*, **110**: 1730, 1938.
114. BUTLER, A. M.: *New England J. Med.*, **243**: 648, 1950.
115. BENSLEY, E. H., STEPHENS, J. W. AND WOOD, P.: Unpublished data.
116. HERRINGTON, M. S.: *J. A. M. A.*, **108**: 1339, 1937.
117. BUTLER, A. M., TALBOT, N. B., CRAWFORD, J. D., MACLACHLAN, E. A. AND APPLETON, J.: *Am. J. Dis. Child.*, **72**: 481, 1946.
118. TARAIL, R.: *Am. J. Med.*, **6**: 828, 1948.
119. MERRILL, J. P., LEVINE, H. D., SOMERVILLE, W. AND SMITH, S. III.: *Ann. Int. Med.*, **33**: 797, 1950.
120. BYWATERS, E. G. L.: *J. A. M. A.*, **124**: 1103, 1944.
121. KOLFF, W. J.: New Ways of Treating Uræmia; the Artificial Kidney, Peritoneal Lavage, Intestinal Lavage, J. & A. Churchill, London, 1947.
122. MACLEAN, J. T., RIPSTEIN, C. B., DELEEUW, N. K. M. AND MILLER, G. G.: *Canad. M. A. J.*, **58**: 433, 1948.
123. IRWIN, L., BERGER, E. Y., ROSENBERG, B. AND JACKSONTHAL, R.: *J. Clin. Investigation*, **28**: 1403, 1949.
124. DANOWSKI, T. S., GREENMAN, L., MATEER, F., PETERS, J. H., WEIGAND, F. A., MERMELSTEIN, H. AND CLARKE, C. E.: *J. Clin. Investigation* (Proc.), **29**: 807, 1950.
125. ELKINTON, J. R., CLARK, J. K., SQUIRES, R. D., BLUEMLE, L. W. JR. AND CROSLEY, A. P. JR.: *Am. J. M. Sc.*, **220**: 547, 1950.

SPINAL ANALGESIA WITH HYPOBARIC PONTOCAINE FOR CÆSAREAN SECTION*

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THERE EXISTS today a great variance of opinion regarding the indications for spinal anæsthesia or spinal analgesia in cases requiring Cæsarean section. The danger of intercostal paralysis, where the diaphragm is splinted with a gravid uterus at or near full term, has caused many anæsthetists to avoid this method of anæsthesia. A method of spinal analgesia will be outlined which reduces this hazard, resulting in adequate sensory analgesia with a minimum of motor involvement.

The anæsthetic agent used is pontocaine in a hypobaric solution. Lund and Cameron[1] described the use of 0.1% pontocaine in distilled water and reported satisfactory results in providing spinal anæsthesia for abdominal, urological and lower limb surgery. This solution was used for Cæsarean section and it was noted that a variable degree of motor anæsthesia resulted. It was our impression that the motor anæsthesia was of shorter duration than expected with that dose of pontocaine. The dilution of pontocaine in distilled water was then increased to 0.066%. This was prepared by adding 5 c.c. of distilled water to 10 c.c. of 0.1% pontocaine. The original dosage was 10 mgm. pontocaine in 15 c.c. water. This has gradually been reduced and the dosage now employed is 6 mgm. pontocaine in 9 c.c. distilled water. This is also prepared by adding 3 c.c. distilled water to 6 c.c. 0.1% pontocaine. The specific gravity of this solution is 1.0015 at 26° C.

Clinical technique. — All patients were seen preoperatively and considerable time was spent explaining the procedure to them. They were given time to ask any questions regarding their pending operation and anæsthetic. If time permitted nembutal gr. 1½ was given the evening before. In cases of emergency Cæsarean section no barbiturate was given preoperatively. Atropine gr. 1/50 was given 30 minutes before the spinal puncture.

A vasopressor was used in each case in this series. Methedrine 10 or 20 mgm. was injected subcutaneously 10 minutes before the administration of the pontocaine. The patient was not taken into the operating room until it was completely set up. The surgeon and his assistant scrubbed and entered the operating room with the anæsthetist to avoid delay in starting the Cæsarean section after the anæsthetic solution was injected into the subarachnoid space.

The patient was placed in a sitting position on the operating table. The head of the table had previously been slightly lowered. Lumbar puncture was made with a 21 or 22 gauge needle at the interspace between the third and fourth lumbar vertebræ. Injection time was approximately 18 sec. and the total time the patient sat up after the initiation of the injection was never over 25 seconds. As soon as the patient was lying in slight Trendelenburg position an intravenous infusion was started. Simultaneously the surgeon prepared the patient and made the incision. After the baby was delivered and the mother saw her child, a 2.5% solution of pentothal in small repeated doses was added to the intravenous infusion.

*Presented at the 1951 meeting of the Ontario Medical Association.

RESULTS

This series is composed of 55 cases. They are consecutive cases in which there was no specific indication for a general anæsthetic. Truthful and deliberate reassurance resulted in a patient arriving at the operating room relaxed and confident. Spinal analgesia was accepted without fear.

The height of sensory analgesia varied primarily with the amount of drug used, the duration of injection time and total time the patient was left in the sitting position. Total sensory analgesia occurred in some of our early cases where the large dose of pontocaine was used. With the smaller dosage the patients usually felt the pain caused by an Allis clamp over the area supplied by the cutaneous branches of the cervical plexus.

Respiration has not been embarrassed. Intercostal paralysis could not be demonstrated above the ninth thoracic segment. In those cases where a 6 mgm. dose was used, the patients could, with the exception of one, move their toes during the surgical procedure.

The duration of analgesia is difficult to predict. During the early cases in this series, if a patient requested that she be allowed to stay awake, pentothal was withheld. Of the first 23 cases 15 remained conscious without experiencing pain during the operation. This required from 45 minutes to 65 minutes. The remaining 8 felt pain after 34 to 60 minutes, and pentothal was given. As a result of this variance, pentothal is now given to all patients after they see their babies. Adequate analgesia is established by the time the patient is draped. Care is taken so that there is no delay from the onset of analgesia to the time of incision. This has allowed an abundance of time for resuscitation and cleaning of the baby before the mother sees it.

When the patient has been properly informed, there have been no complaints about the sensation of pressure which occasionally occurs, particularly when the surgeon presses the fundus during delivery.

The preoperative blood pressures in all cases in this series were within normal limits. Hypotension did not present a great problem. In two cases there was a drop in systolic pressure of 50 mm. of mercury or more. The normal pressure in these was re-established with the use of intravenous methedrine. Four cases had a drop in systolic pressure of 10 to 49 mm. This was also controlled with methedrine.

Hypertension presented a problem, particularly in the early cases where an initial dose of 20 mgm. methedrine was given 10 minutes before the lumbar puncture. Fourteen cases had a rise of 50 mm. mercury or more in systolic pressure. It was this which led to the reduction of the initial dose of methedrine to 10 mgm. It is proposed that in future the lumbar puncture will be done without first giving a vasopressor drug subcutaneously and that the vasopressor drug will be administered in small repeated intravenous injections, if indicated.

Nausea and vomiting occurred in six cases during the operative procedure. Two patients developed headache, one of which concurrently developed infectious hepatitis. One patient with rheumatic heart disease developed pulmonary œdema which was controlled with positive oxygen pressure. There was no maternal mortality. There were no other complications.

There were two babies dead at time of delivery. In one instance death was due to congenital abnormalities, and in the other the fetal heart could not be heard before operation. A third premature child died on the second day following aspiration. The remainder left the hospital in good health.

It is regretted that no accurate records were kept on resuscitation time. It is our impression that the majority of babies cried spontaneously when delivered. It was noted that there were no periods of anoxia in the newborn of sufficient duration to warrant recording.

CONCLUSION

Greater protection is given to the mother with the use of smaller amounts of pontocaine in a more dilute solution. The duration of analgesia, although not as long as with the more concentrated solutions, in sufficient. Respiratory embarrassment has not resulted from intercostal paralysis. Hypotension is controlled with small doses of a vasopressor drug, and/or Trendelenburg position. The incidence of complications has been very small.

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REFERENCE

1. LUND, P. C. AND CAMERON, J. D.: *Anæsthesiology*, 6: 565, 1945.

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UNILATERAL RENAL AGENESIA*

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UNILATERAL RENAL AGENESIA, or congenital solitary kidney is a problem of major clinical importance. In this presentation I am referring to cases where there is only one demonstrable kidney. This condition must be differentiated from aplasia, hypoplasia, contracture due to pyelonephritis, crossed ectopia and, of course, the results of renal surgery. It is not the intention to discuss the embryological causes; this has been well done by Nation; also, a good review of the subject is in Rolnick's recently published work. Informative studies have recently been published by Smith and Orkin, and Benjamin and Tobin.

A study of the literature reveals that all reports are based on small series of cases. These observations on eight cases may therefore be of some value.

A criterion for diagnosis must be established. It is freely admitted that the only absolute diagnosis is one made at autopsy. However, in justice to our patients we must accept reasonable findings. These findings must show, first, the absence of any renal shadow, second, failure to demonstrate a kidney, by cytoscopic study plus dye tests, and by pyelography, retrograde and intravenous. The presence of two ureteral orifices does not rule out the condition, because one may belong to a vestigial ureter. Neither is the presence of only a single ureteric orifice in itself sufficient for a sure diagnosis.

I submit the following summaries:

CASE 1

P.K., Chippewa Indian, aged 48, referred in 1931 by Dr. J. C. Gillie with history of frequency and difficulty of urination. The right kidney was easily palpated below the level of the umbilicus; it was smooth and fixed but was not tender. No left kidney was palpable. Prostate large, residual urine 2½ oz. B.P. 128/80. Urine, trace of albumen. P.S.P. intravenously appeared in 4 minutes, 40% excretion in 30 minutes. Blood urea 21 mgm. %.

Cystoscopic examination: An F. 24 cystoscope entered the bladder with little difficulty. The bladder was of good capacity, no ulceration or calculi present. There was marked intravesical prostatic enlargement. The right ureteral orifice was easily seen and was normal in all respects. A prolonged search revealed no sign of the left orifice, the left side of the trigone appeared to be flattened out and there was no sign of the inter-ureteric ridge on that side. The right ureter was catheterized easily and indigo carmine injected intravenously. It appeared in the right urine in 4 minutes and continued in good concentration. A 30 minute search failed to show any dye from the left side. Microscopic examination of the right catheter specimen showed only a few epithelial cells.

The right kidney and ureter were visualized by uroselectan but no trace of anything was seen on the left. The dome of the bladder was drawn to the right.

Cystoscopy was repeated and again no trace of the left orifice was visible. A right pyeloureterogram was made, 22 c.c. of sodium iodide being injected without pain. This showed a uniformly large pelvis and calyces with good cupping. The ureter was uniformly enlarged and somewhat angulated. The kidney shadow was extremely large, extending from the level of the lower third of the 12th dorsal to near the base of the 4th lumbar vertebræ. No trace of the left kidney shadow was visible on any of the several plates.

At operation the bladder was widely opened and inspected, digitally and visually. The thickening around the right orifice was palpable but on the left side the corresponding region was smooth. The prostate was enucleated without difficulty.

In 1950 he reported that he was in good health: he had married one year after his operation and had one child.

CASE 2

G.M., male, aged 36, referred by Dr. E. D. Rathbone. Patient was admitted to hospital with right epididymo-orchitis. General examination showed congenital amputation of the left thigh and complete absence of left scrotal contents. Intravenous pyelogram showed normal right kidney and ureter with distortion of bladder and no evidence of left kidney shadow. When infection was eradicated cystoscopy revealed a badly distorted bladder; five minutes after intravenous injection of indigo carmine a ureteral orifice was detected on the right lateral wall close to the internal orifice. Catheter was passed, fifteen minutes observation revealed no other sign of dye. Retrograde pyelogram confirmed intravenous pyelogram.

This is an example of renal agenesia with multiple congenital anomalies.

CASE 3

D.McB., age 22, referred by Dr. C. E. Baker. This young man, a motor mechanic, had a minor accident and complained of some lower left abdominal pain. An intravenous pyelogram showed no shadow on the left side. At cystoscopy the right ureter was catheterized easily, a catheter went up the left ureter about 3 cm. Indigo carmine appeared on the right side in three minutes with excellent concentration. No dye came down the left side. Retrograde pyelogram showed large normal shaped kidney and only about three inches of a thready left vestigial ureter.

CASE 4

L.I., male, aged 45, patient of Dr. J. D. Markham. The patient was in hospital in the terminal stages of general carcinomatosis with the primary lesion in the pancreas. There was complaint of pain in the right loin. As wasting progressed a mass was detected. Intravenous pyelogram demonstrated a deformed right kidney and no renal shadow on the left side. It was felt that the kidney was involved in his general carcinomatous disease. Autopsy revealed a congenital solitary kidney with a secondary neoplastic lesion.

CASE 5

M.C., male. Referred by Dr. Watsyk with history of pain and frequency at intervals for the previous three years. Gunshot wounds in first war involving thigh and scrotal contents. Urethral stricture had to be treated before cystoscopy possible. Cystoscopy showed bladder of good capacity with marked congestion. Left ureter easily located and catheterized, the right side of bladder was flattened out and no ureteral orifice was found. Indigo carmine showed good concentration from left catheter, no dye was visible in the bladder. Pyelogram showed

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a filling defect in upper calyces. No right renal shadow was seen. Intravenous pyelogram confirmed the above findings. Smear showed Gram-positive cocci, culture, no growth: examination for T.B. was negative. The man was told that he had a solitary kidney with severe infection but he was of the suspicious type. He was examined by several others and finally cystoscoped by Dr. Crompton of Toronto in October 1941, who commented, "I could not find a right ureteral orifice on cystoscopy nor did the dye show up in the right side with an excretory urogram. Also there was no visible renal outline on that side." Guinea pig inoculations were positive for tuberculosis. Sanatorium care was advised, patient refused and finally entered Sanatorium on August 31, 1942 with disseminated tuberculosis and died on October 29, 1942. No autopsy was obtained.

CASE 6

Mr. L., aged 37, (courtesy Dr. A. E. Allin, April, 1943). Cause of death: accidental electrocution. At autopsy he was found to have only one kidney, the right. This measured 13 cm. in length, 7.6 cm. in width and 6 cm. in thickness. It appeared to be relatively near its normal position although perhaps somewhat shifted towards the mid-line. The only abnormality noted was the renal vein, which measured only 1 cm. in length. The right adrenal was normal. On the left side the kidney was absent; the suprarenal appeared normal; no ureter was detected. Unfortunately no particular attention was paid to examining the bladder for indications of vestigial ureter.

CASE 7

N.W., male, aged 59, referred by Dr. C. R. McComb. This man weighed 187 lb. and was in general good health. He served throughout first Great War in the British Navy. Patient was referred May 26, 1949 for frequency, with urine showing pus and blood. Prostate small, no residual.

Cystoscopy: bladder good capacity, left ureteral orifice normally placed, somewhat gaping, catheterized easily, no evidence of a right orifice was found, right region of trigone flattened out, indigo carmine appeared in left urine in 3 minutes with good concentration. No dye was seen elsewhere after twenty minutes' observation. Pyelogram revealed calculi in a large left kidney and shadow of a small stone in lower end of left ureter. No shadow of a right kidney was seen. An intravenous pyelogram confirmed these findings.

Watchful waiting was advised. Late in June the patient was upset with indefinite discomfort. Under spinal the ureter was dilated, one attempt was made with the basket but stone was not recovered. On August 19 patient passed one small stone and in September three others. Seen early in 1951 he reported his condition satisfactory.

CASE 8

I am indebted to the D.V.A. for permission to include the following case in my series.

R.W., born October 31, 1917, enlisted April 13, 1942, Category A1. In June he first became conscious of some pain in the right side, this was not severe and was ignored until October when he reported to R.M.O. During the spring of 1943 the pain was aggravated by motor cycle riding and while not severe or disabling it radiated to the groin. Examination of urine revealed albumen and he was admitted to No. 15 General Hospital for study on April 20, 1943. Study with retrograde and intravenous pyelograms revealed calculi in the right kidney. The right kidney was enlarged, no left kidney was demonstrated and a catheter entered left ureter one inch only and after injection only three inches of a very narrow ureter was visualized. A diagnosis of congenital solitary kidney with calculi was made and the patient was boarded out. He was in Deer Lodge Hospital, Winnipeg from July 7 to July 24, 1943 where the diagnosis was confirmed and conservative treatment advised. He was in Christie Street Hospital, Toronto, from November 11 to December 12, 1943 and February 3 to March 10, 1944 where study was repeated with the same observations. On his last admission there is record of moderate infection. The records show that observation plus medication for infection was advised.

He was again in Deer Lodge Hospital from August 14 to September 17, 1945, being admitted after a bout of high fever and right sided pain. This subsided under sulfathiazole. At that time he showed persistent R.B.C. and W.B.C. in urine with positive albumen. Blood urea 12.1 mgm. He was discharged and advised to remain where he could get attention if an emergency developed.

I saw him first in November 1945 during a severe attack of colic with fever. Urine culture showed presence of *B. pyocyaneus*. He responded to medical treatment. He was admitted to hospital again on November 13, 1946 with severe colic and fever. There was no relief from pain by sedative. I therefore concluded that one of the stones was impacted at the ureteropelvic junction. I stood on the bed, took the patient's knees over my shoulders and rapped his head on the floor a few times. When I stretched him out he reported the pain gone. Urine culture again showed *B. pyocyaneous*. He was treated with sulfadiazine and left hospital with negative culture. He had further attacks of colic in November and December 1946 and January 1947 and on February 17, 1947, was hospitalized with a severe attack of colic and fever. X-ray revealed that the stones were rapidly increasing in size. This with the short interval between severe attacks of colic and the fever and infection made surgical intervention imperative.

On February 25, 1947 I operated through the usual lumbar incision finding a large kidney imbedded in a pad of perirenal fat. There were dense adhesions at the lower pole. When these were released a normal ureter was found, this was traced upwards and led to an anterior pelvis. With some difficulty the kidney was separated from the peritoneum without damage and an average sized pelvis exposed. The pelvic wall was thickened, it was opened and seven stones were recovered. Finger examination revealed large smooth calyces. An x-ray was taken and while this was being developed another search for stones was made and one more recovered. The radiologist reported one stone on his film and as I had recovered one after the picture was taken and could find no other the pelvis was sutured and the wound closed with drainage. The patient left the hospital in good condition on March 15, with wound finally dry on March 22. There was no pain or discomfort, no frequency, the urine constantly showed a few pus cells and a variety of organisms were cultured in succession. Finally on May 31 the urine showed only an occasional pus cell and was negative on culture. Patient was advised to continue acid ash diet, dalitol and extra fluid intake.

During the fall of 1947 patient had some vague discomfort in the right side. Deer Lodge suspected calculi. A low degree of infection was constantly present in the urine. In December 1947 patient was seen with sudden acute pain in left testes, during examination and manipulation pain suddenly eased. A tentative diagnosis of torsion of the testes was apparently confirmed. X-rays at that time revealed shadows of two small renal calculi. November 1948, at check up in Deer Lodge, findings of stones and infection confirmed. On his return home he was given a course of streptomycin and urine again became negative. In August 1949 he reported with some pain and fever. Urine again infected, treated medically. Urine became negative again and remained so during September under mandelamine. February, 1950 reported with severe pain in the right inguinal region and the following day had a right epididymitis, treated with streptomycin and intravenous sodium iodide. In two weeks he was back at work with negative urine. In April 1950, after slight pain, he passed several small stones a little larger than a pin head, followed by complete relief. In February 1951, examined at Deer Lodge, no symptoms, some tenderness on deep palpation. Urine showed pus and R.B.C., culture *B. pyocyaneus*, resistant

to penicillin, aureomycin and chloromycetin but sensitive to terramycin. Blood urea nitrogen 19 mgm. X-ray showed at least four stones in renal pelvis, pyelogram showed some increase in size of calyces.

I saw the patient again in April 1951. He had no complaints and had every appearance of being in good health. I am deeply indebted to Dr. David Swartz for his co-operation over the years in connection with this patient.

SUMMARY

All my cases were found in male adults although over 60% of my urological patients are female.

The right kidney was absent in two cases, the left absent in six cases.

The ages when first seen were from 22 to 59 with an average age of 40 years.

Seven cases were diagnosed clinically. This includes one where a tentative diagnosis was confirmed shortly by autopsy. Of six cases thoroughly studied five are alive at the time of this presentation. One case was a pure autopsy finding after a death by accidental electrocution. In only one of the eight cases were non-urinary congenital anomalies detected.

Two cases had short vestigial ureters. In one case the only orifice present was near the midline. In three cases the trigone was flattened out on the affected side. Two cases were complicated by calculi.

Urologists must constantly emphasize the necessity for careful study before any renal surgery is performed. They themselves are not likely to operate upon these or similar cases, but I have known a general surgeon of professorial rank to do a nephrectomy, in recent years, without cystoscopic study, with a fatal result.

BIBLIOGRAPHY

1. NATION, E. F.: *Surg., Gynec. & Obst.*, 79: 175, 1944.
2. ROLNICK, H. C.: Practice of Urology, Lippincott, p. 618, 1949.
3. SMITH, E. C. AND ORKIN, L. A.: *J. Urol.*, 53: 11, 1945.
4. BENJAMIN, J. A. AND TOBIN, C. E.: *J. Urol.*, 65: 715, 1951.

PAIN ABOUT THE RADIAL STYLOID*

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THE COMPLAINT OF PAIN in the region of the radial styloid is not infrequently encountered in practice, and its most common etiological basis is trauma. This may be acute and take the form of a direct blow or, on the other hand, may proceed from a single forceful abduction. Most often, however, it is chronic in nature and examples of this are legion. The patient has usually been engaged in occupations requiring the use of the thumb in repetitious motions against resistance, such as operating a typewriter, playing a piano, folding boxes, operating a buffing or grinding machine or carrying trays of dishes. It is very frequently diagnosed as arthritis of the wrist joint.

Perhaps the most frequently encountered and best recognized condition in this area is stenosing tenosynovitis at the radial styloid or De Quervain's disease. This condition was first described by De Quervain in 1895. Following this, several articles appeared in the European literature discussing this problem, but it was not until 1927 that any mention of it appeared in the American journals. In that year Stein[1] discussed 5 cases. In July 1928 Schneider[2] described 15 cases of his own in which he advocated conservative treatment in early cases and cited 8 cures by this method. He advised surgical treatment for chronic cases. In 1930 Finkelstein[3] published a review of 24 cases successfully treated by operation. In addition he presented some experimental work done on rabbits in which he proved that the condition could be produced experimentally. In 1944 Lipscomb[4] published an exhaustive study of the subject and more recently Patterson and Jones[5] reported on this condition and advocated surgical intervention. In 1948 Murphy described two unusual cases in which only the tendon of the extensor pollicis brevis was involved.

Anatomy.—The tendons usually involved are the short extensor of the thumb and the abductor pollicis longus. These tendons traverse a groove in the lateral aspect of the distal end of the radius and are retained in it by the annular ligament, which forms a separate compartment for them. They are also surrounded by a sheath which extends above and below the annular ligament. In some cases the tendons are enclosed in separate sheaths and may also occupy separate compartments under the annular ligament. In addition a third tendon may occasionally accompany the other two.

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Proceeding downward side by side and closely applied to the lateral aspect of the radius are the extensor carpi radialis longus and brevis. They are crossed obliquely by the above-mentioned two tendons about the junction of the middle and lower third of the forearm and pass in a single sheath beneath the extensor retinaculum. They groove the distal end of the radius and are inserted into the bases of the second and third metacarpals.

Pathology.—As a result of the trauma whether acute or chronic the tendon and sheath become congested and undergo roughening with deposition of fibrin. This later organizes and may become hyalinized, and in rare cases may even undergo cartilage formation. The usual end result is a thickening of the sheath or the tendon which interferes with the movement of the tendon and gives characteristic pain.

Symptomatology.—The patient complains of pain on the radial side of the wrist which may radiate up into the arm and down into the thumb. The pain is aggravated by use and in the case of De Quervain's disease, movements of the thumb into abduction and the wrist into adduction increase this pain. Lipscomb states that the pathognomonic sign of De Quervain's disease is a sharp pain elicited if the thumb be held against the index finger and the wrist forced into adduction.

It is unusual for snapping to occur in De Quervain's disease although other tendons similarly involved may exhibit this phenomenon. In one of our cases snapping thumb was present.

Treatment.—Conservative treatment may be tried but it is usually of little avail, with either no improvement or at best, minimal improvement. This mode of handling the condition is accomplished by immobilizing the wrist by splint or cast where heat and physiotherapy has failed. Even when some improvement has occurred, return to work usually means a recurrence of symptoms.

Surgical treatment offers complete relief and there are no recorded cases of recurrence. The tendons are exposed through a transverse incision over the radial styloid and the involved sheath incised. This alone may suffice, while in other instances it may be necessary to excise a portion of the sheath in order to allow free movement of the involved tendon. While this is the best recognized form, any tendon sheath about

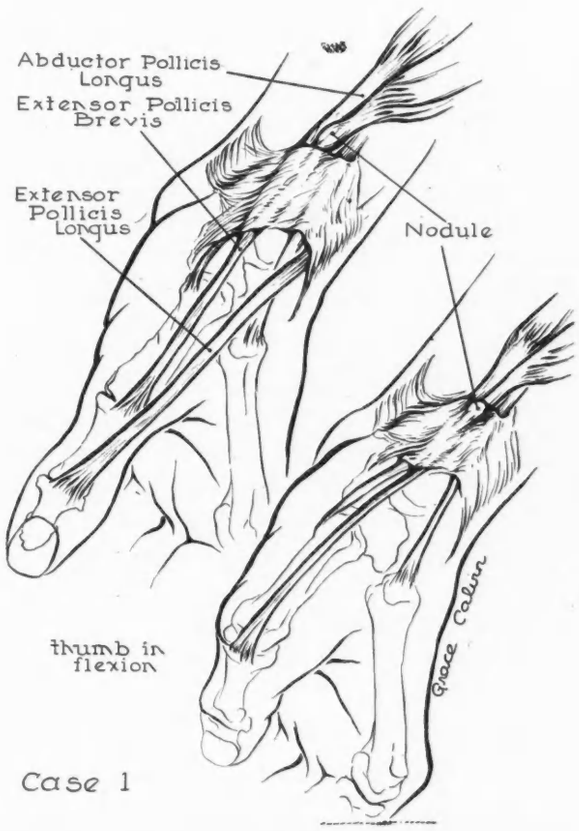

Fig. 1

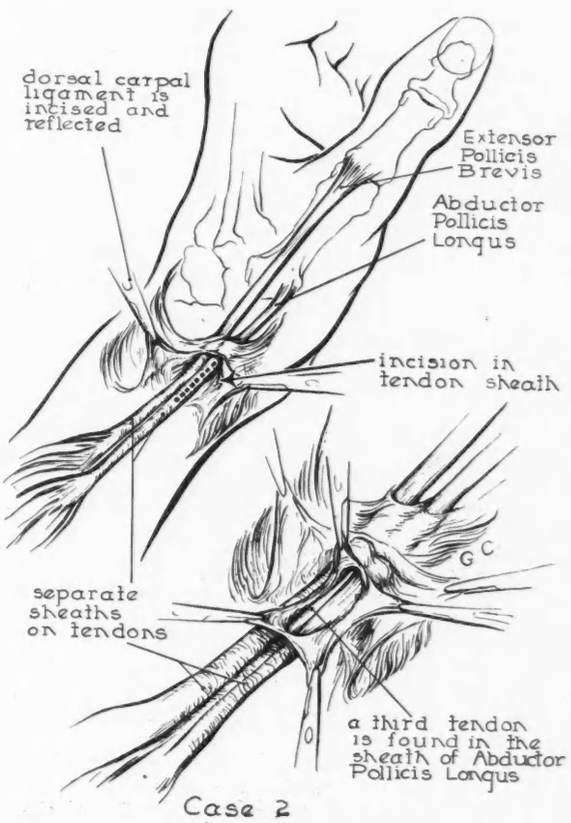
dorsal carpal ligament is incised and reflected
Extensor Pollicis Brevis
Abductor Pollicis Longus
incision in tendon sheath
separate sheaths on tendons
a third tendon is found in the sheath of Abductor Pollicis Longus
Case 2

Fig. 2

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the wrist may be involved and cause aching and pain in the wrist. The involved tendon can be determined by the site of the tenderness and the motion which causes pain.

We have recently encountered three cases all of which presented unusual features.

CASE 1

One month following confinement this patient began to experience aching in the region of the left radial styloid. This increased in severity but at this time the pain could not be definitely localized to the abductor pollicis longus or the extensor pollicis brevis. The pain was aggravated by the carrying of a large container which was habitually used in filling the baby's bath. About six months after the onset of symptoms a snapping developed, accompanied by pain which recurred with movements of the thumb.

Almost a year later the long abductor and the short extensor were explored through an incision on the radial side of the lower forearm. A nodule 0.8 cm. in diameter was demonstrable in the tendon of the extensor pollicis brevis. On full flexion of the thumb this disappeared under the dorsal carpal ligament with a sharp snap. A portion of this ligament was then excised sufficiently so that the nodule was completely free even on full flexion. Immediately following the operation the patient was symptom-free and has so remained up to the present time.

CASE 2

This patient presented the classical symptoms of pain over the radial styloid radiating up into the forearm which had been present for a month. Movement of the thumb and in particular, abduction, aggravated the pain. Examination revealed tenderness over the tendons at the radial styloid. Crepitus was apparent with movements of the thumb.

Exploration of the tendons was carried out. The usual condition found was that the tendons of the extensor pollicis brevis and the abductor pollicis longus were enclosed in separate synovial sheaths and lay in separate compartments under the dorsal carpal ligament. These sheaths showed moderate thickening. On opening the sheaths a third tendon about 0.3 cm. in diameter was found in the sheath of the abductor pollicis longus. This united with the tendon of the abductor pollicis longus at the point where it passed under the dorsal carpal ligament. The superficial portion of both sheaths was freely excised. The patient returned to her work in two and one half weeks, free of symptoms and has remained so up to the present.

CASE 3

This patient, a miner, was struck by a rock on the lateral aspect of his forearm just above the wrist. X-rays were taken and were negative and a cast was applied. He was seen by us sixteen days later at which time pain was still present on the postero-lateral aspect of the forearm and particularly on movements of the wrist and thumb. There was some swelling in this area and it was tender on palpation. In addition a fine crepitus was noted with movements of the thumb. Further x-rays were taken and showed an area of light calcification 10 cm. above the distal end of the radius. A diagnosis of De Quervain's disease was made and, since the patient had all that conservative treatment could offer without result, we admitted him to hospital for exploration of the forearm.

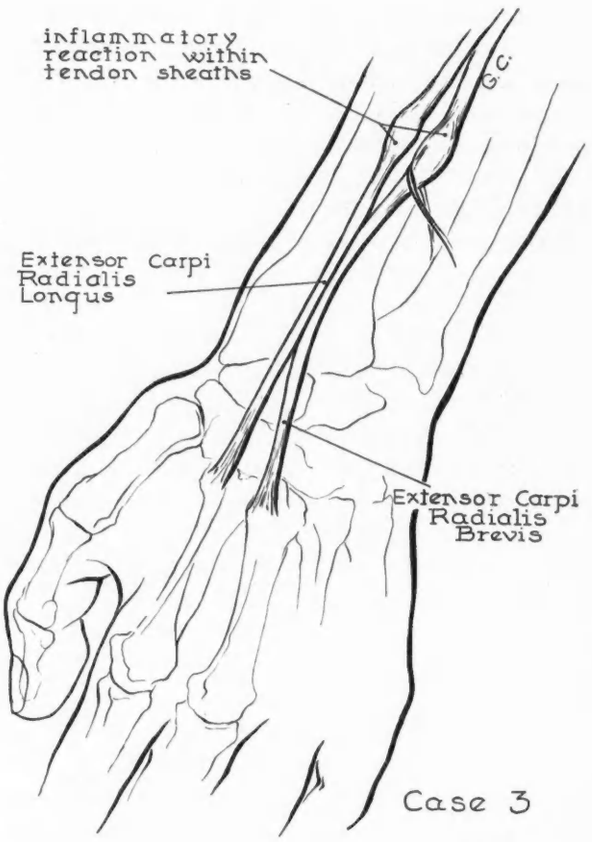

Fig. 3

At operation the short thumb muscles were found to be normal. There was, however, an area of inflammatory reaction in the sheath of the extensor carpi radialis longus and brevis about 3 inches above the radial styloid. The sheath was freely excised and the wound closed. Now, four months after operation, the patient has full use of wrist and thumb without pain.

DISCUSSION

It is unusual, though not unreported, for tendons involved in stenosing tenosynovitis at the radial styloid to exhibit the phenomenon of snapping. This is usually encountered, however, in stenosing tenovaginitis of the flexor tendons of the hand. In the second case the finding of the third tendon as described above presents an unusual feature although Lipscomb states that in their series to date it is quite usual and may be of etiological significance.

REFERENCES

1. STEIN, J. B.: *Am. J. Surg.*, 3: 77, 1937.
2. SCHNEIDER, C. C.: *Surg., Gynec. & Obst.*, 46: 846, 1928.
3. FINKELSTEIN, H.: *J. Bone & Joint Surg.*, 12: 509, 1930.
4. LIPSCOMB, P. R.: *Surg. Clin. North America*, 24: 780, 1944.
5. PATTERSON, D. C. AND JONES, E. K.: *Am. J. Surg.*, 67: 152, 1945.

KERATOSIS OF THE LARYNX WITH PROGRESSION TO MALIGNANCY*

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LARYNGEAL KERATOSIS is a rare condition characterized by irregular areas of thickening and cornification of the laryngeal mucous membrane. Much controversy exists regarding its etiology, treatment and terminology. Some authorities interchange the term "keratosis laryngis" with that of "leukoplakia" of the larynx, and with "pachydermia laryngis". There are however, others who believe that these terms are not interrelated.

This paper will attempt to describe some of the more characteristic features of the disease. A case report will be presented to emphasize the problems of treatment.

Jackson and Jackson[1] describe "pachydermia laryngis" as being a tumour-like, non-ulcerating, lesion which usually begins in the posterior commissure and extends to involve varying amounts of the laryngeal mucosa. Virchow originally described this condition and inferred that pachydermia laryngis was a disease entity distinct from leukoplakia laryngis and keratosis laryngis. We are inclined to agree with Clerf's[2] belief that "pachydermia laryngis", leukoplakia of the larynx, and keratosis laryngis, are interchangeable terms which describe varying stages of the same disease process. Histopathologically the findings in all three conditions are identical.

Lederer[3] describes three types of pachydermia laryngis, depending on whether the gross lesion is a uniform thickening (pachydermia laryngis diffusa), or whether there are areas of warty elevation (pachydermia laryngis verruca), or a combination of both.

ETIOLOGY

Clerf[2] quotes Reimann's theory that keratosis is "a disease of shedding of the superficial layers. These cells do not differentiate as do normal cells, but stick together, pile up and produce the islands we call keratinized because of an excess of keratin in the cell".

Little is known about the cause of this disease although many theories have been postulated. Some of the better known are enumerated here: (1) Tobacco. (2) Excessive use of alcohol. (3) Vocal abuse. (4) Chronic postnasal discharge with laryngeal irritation. (5) Syphilis. (6) Endocrine dyscrasia. (7) Dietary deficiencies with low vitamin A and B intake. (8) Virus infection. (9) Mycosis.

SYMPTOMS AND SIGNS

Painless hoarseness is the chief symptom. Occasionally there may be associated cough, dyspnœa and stridor.

The objective mirror examination is characteristic. One observes discrete or confluent, flat or papillary, grey-white, irregular patches covering the laryngeal mucosa. The distribution is erratic, although in Virchow's type of pachydermia laryngis the lesion will first be seen to arise in the posterior third of the larynx. These patches may occasionally involve one side only, but more often they are irregularly bilateral in distribution. Usually, there is no ulceration but one may observe strict demarcation between normal mucosa and the borders of involved tissue.

The diagnosis rests in microscopic study which is conclusive. Histopathologically, one finds the laryngeal epithelium thickened, elevated, and keratinized but the basement membrane is intact, although irregular in contour. There is always an inflammatory cell infiltration of the subepithelial tissues.

TREATMENT

Both medical and surgical techniques are usually employed. In general, medical management is based on a variety of therapeutic agents. Some of the more common ones are as follows. The sulfonamide drugs, as well as penicillin, streptomycin and aureomycin have been tried without much success. The antibiotics are administered by aerosol, lozenge, spray and by oral and parenteral methods. Intensive vitamin A, B, and C therapy is supposed to be of value and cures have been described following their employment, in conjunction with laryngeal "stripping" procedures.[4] Exclusion of alcohol, tobacco, and spicy food is considered useful. Complete voice rest. Treatment of concomitant infections of the nose, sinuses and throat is always well advised.

Deep x-ray therapy has been employed and cures have been reported from its use. However, some laryngologists believe that deep x-ray ther-

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apy should be withheld on the ground that the keratosis laryngis condition may at any time degenerate into carcinoma and this might interfere with laryngectomy, if and when it should be performed. Others fear the complications of perichondritis of the larynx and laryngeal stenosis which occasionally may result from deep roentgen therapy, particularly since 80% of these lesions are supposedly benign. It was New and Erich[5] who observed that 20% of patients with keratosis laryngis eventually developed carcinoma.

From the surgical viewpoint, "stripping" of the involved laryngeal mucous membrane is considered the treatment of choice. Technically this procedure may be carried out with the aid of the Roberts retention laryngoscope, the Lynch suspension laryngoscope, laryngeal forceps, and local or general anæsthesia. Jackson's direct laryngoscopes are employed by many laryngeal surgeons, but we prefer the Roberts or Lynch instruments for this operation since it allows the surgeon the use of both his hands for stripping the mucous membrane.

The "stripping procedure" should be performed as often as indicated, and, this is determined by the rate at which the lesion reappears on the cords. It is customary to combine this procedure with intensive medical treatment as previously outlined.

CASE HISTORY

T.J., a 49 year old white male, was first treated in June 1946, for hoarseness of two weeks' duration. Indirect mirror examination revealed a "heaped-up" area over the right arytenoid. Direct laryngoscopy and biopsy from this region was reported as follows: "Hypertrophy of squamous epithelium, beneath which the fibrous tissue of the tunica propria is intensely œdematous. In this layer there is present a moderately intense diffusion of inflammatory cells consisting of lymphocytes, plasma cells and neutrophilic polymorphonuclear leucocytes." The diagnosis was hypertrophic laryngitis.

He was treated by steam, voice rest, vasoconstrictors locally, and sulfadiazine by mouth but there was little improvement in his hoarseness.

Eight months later, in February 1947, indirect and direct laryngeal examination revealed white plaques on the right true vocal cord, and right false cord. Histopathologically, these plaques were reported as follows: "The squamous epithelium is hypertrophic, thickened, and reveals bulbous rete pegs protruding into the tunica propria. These pegs are of a mature, well differentiated, prickle cell type. There is a well developed stratum granulosum, several cell layers in thickness, and these cells contain many basophilic keratohyaline granules. The entire epithelial surface is covered by a thick acellular stratum corneum which has an irregular outline". Diagnosis was keratinizing hypertrophy of the mucous membrane of the larynx (Fig. 1), *i.e.*, keratosis laryngis.

About this time, the patient departed for another city, and he next returned to the clinic in January 1949, when he complained of persistent hoarseness. He had received no treatment during this two year interval. There was

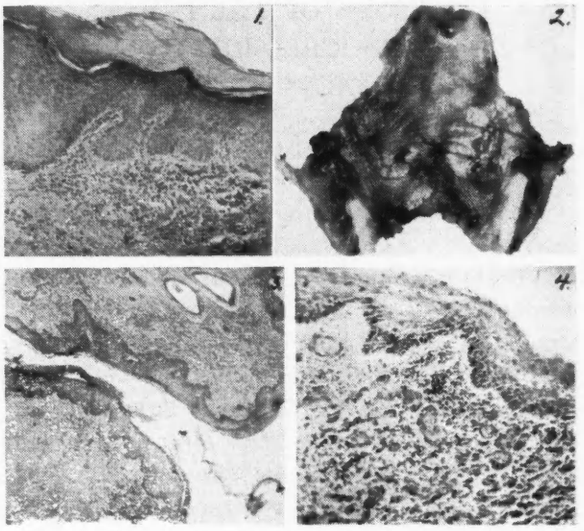

Fig. 1.—Biopsy of left side of larynx, February, 1947, x 100. Acanthotic hyperplasia of squamous epithelium with well developed stratum granulosum and corneum. Hyperæmia and chronic inflammatory reaction in the tunica propria. **Fig. 2.**—Mucosal aspect of the larynx opened posteriorly to illustrate the white, "warty", mucosal plaques and the extent of the involvement. **Fig. 3.**—Left true and false vocal cords, x 40, illustrating the thick, keratinized epithelium over both cords and the subepithelial chronic inflammatory reaction. **Fig. 4.**—Right true vocal cord, x 100, in an area of microscopic infiltrating epidermoid carcinoma.

no pain, no weight loss, and no neck nodes associated with the deep toned voice. Indirect and direct laryngeal examination revealed white, thick patches in the region of the right true vocal cord, ventricle, and right arytenoid. Both true vocal cords moved well in adduction and abduction. Biopsy report was pachydermia laryngis. No malignancy. His medical work-up was non-contributory. Blood Wassermann, sinus x-rays, and blood count were all normal.

He was treated by voice rest, steam, vitamin A, B, and C in large doses, penicillin sprays locally and by intramuscular penicillin, but no benefits were observed from these treatments. "Stripping" the laryngeal plaques was then resorted to, with the aid of the Roberts retention laryngoscope and local anæsthesia.

In April 1949, after repeated "stripping" of the diseased laryngeal epithelium, and in spite of the intensive medical measures employed, it was obvious that the disease was still flourishing uncontrolled. The lesion had spread to involve most of the laryngeal vestibule, and both true vocal cords. In an attempt to obtain complete laryngeal rest, a tracheotomy was performed, but this, too, had very little effect on the disease process.

The patient was examined at regular intervals for the following eighteen months. Little change in the larynx was observed, either subjectively or objectively. From time to time, laryngeal biopsies were taken and were reported as "leukoplakia" or keratosis of the larynx, with no evidence of malignancy. Aureomycin was administered by direct application and by mouth, but no beneficial effects resulted.

In October 1950, on routine mirror examination, the right true vocal cord seemed more thickened and irregular in outline. Biopsy from this region was reported as follows: "The hyperæmia and chronic inflammatory exudative reaction are well marked in the tunica propria. The covering squamous epithelium reveals warty hyperkeratosis and acanthotic hyperplasia. There is also hyperplasia in the deeper layers of the epithelium which have become more irregular and atypical. Irregular tongues and buds of cells protrude into the tunica propria. There is evidence of a disarranged polarity. The cell nuclei are relatively enlarged in relation to the cell volume and there is considerable variation in their size. Some have become angular in outline. They contain one large and

occasionally two nucleoli, generally being hyperchromatic and with variable content of granular chromatin. These atypical cell areas reveal scattered mitotic figures and in one high power field, five of these can be identified." A diagnosis was made of intraepithelial carcinoma on the basis of the above cytological and histological irregularities.

In view of the fact that the keratotic plaques seemed to involve the right and left true and false cords as well as the laryngeal ventricles and the epiglottic region, a total laryngectomy was performed even though only one true vocal cord was found to be cancerous in its anterior one-third, by biopsy. The patient made an uneventful recovery, following laryngectomy (Fig. 2). He is being maintained on high vitamin diet indefinitely.

It is not without interest, that on sectioning the excised larynx, there was histopathological evidence of carcinoma in both true vocal cords.

The microscopic study is described hereunder in detail: "A diffuse leukoplakia of the laryngeal mucous membrane is observed, and this process involves the orifices of the laryngeal ventricles. There is a thick, irregular, "warty", stratum corneum, which is parakeratotic in focal areas. Throughout the subepithelial connective tissue, (and only mildly affecting the mucosal glands), there is also noted, a non-specific, chronic inflammatory exudative reaction, consisting of lymphocytes, and plasma cells with capillary dilatation and œdema (Fig. 3). In some areas, one finds evidence of hyaline sclerosis of the collagenous connective tissue. On the left side, in the anterior portion of the true vocal cord and particularly on its inferior aspect, there is present an invasive squamous cell carcinoma which infiltrates to a depth midway between mucosal surface and muscle tissue. In some areas, the carcinoma affects and is in continuity with the basal layers of the squamous epithelial covering of the mucosa. One observes small cords and nests of atypical squamous cells. These have enlarged nuclei, variable in size and shape, which contain varying amounts of chromatin and a prominent nucleolus. Within a few of the cell masses there is whorl and pearl formation. On the right side of the larynx, in an identical position to that present on the left side, there is an infiltrating squamous cell carcinoma, similar in extent and in "degree of differentiation" (Fig. 4).

The more proximal epithelium of the true cord exhibits the leukoplakic changes, but in a short extent at the upper border and in the contiguous mouth of the laryngeal ventricle there are cytological alterations believed to be characteristic of an intraepithelial carcinoma, without any invasive character.

A similar alteration is present in the metaplastic and leukoplakic squamous epithelial covering over a wider area of the false vocal cord and in its contiguous ventricular orifice. In some foci, the cellular alterations affect the deeper layers of the epithelium, that towards the surface being more normal in structure and arrangement, while in other areas the changes affect the full thickness of the epithelium and here, the superficial keratinization frequently is lost. The changes are striking in the following respects, there is a disorganization of normal cell polarity, the cell nuclei are abnormally enlarged in relation to the cell volume and vary in size and shape, some being very large and bizarre in outline; nuclear chromatin is coarsened, increased in amount and exhibits a tendency to cluster beneath the nuclear membrane; nucleoli are enlarged and prominent, being generally single but occasionally multiple; and finally abnormal mitotic activity is present, not being abundant but in some instances having an atypical form (Figs. 5 and 6).

In the more posterior segment of the right side, carcinomatous changes of either intraepithelial or invasive type are not noted.

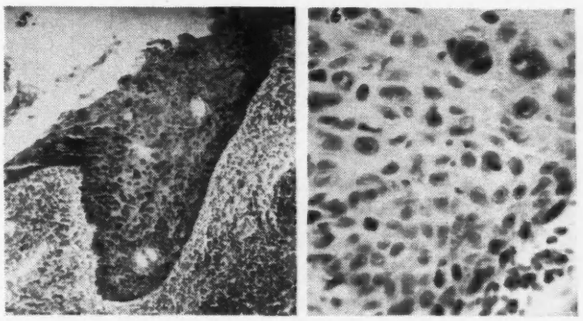

Fig. 5.—Orifice of right laryngeal ventricle, x 100, showing an area of intraepithelial carcinoma with disordered atypical epithelium. **Fig. 6.**—Orifice of right laryngeal ventricle, x 430, illustrating greater cellular detail of the carcinomatous area of Fig. 5.

SUMMARY

The mucosal biopsy specimens of the larynx in 1946 show a non-specific exudative laryngitis. In 1947, the inflammatory process, although less intense, is accompanied by squamous metaplasia of epithelium, with a leukoplakic development of cornification along the surface of the right side. The two biopsy specimens of 1949, show the presence of a well developed leukoplakia in the mucosa of the inter-arytenoid space, the right arytenoid region and right false vocal cord. The leukoplakia is seen in the biopsy specimens of the false cords prepared in 1950, together with cellular changes on the right side which are believed to be those of an intraepithelial carcinoma. With laryngectomy in 1950, the diffuse leukoplakia is confirmed, the presence of fairly extensive intraepithelial carcinoma on the right side of the larynx is substantiated, and unsuspected superficially invasive carcinoma of the infraglottic margin of the true cords bilaterally is recognized.

A case of keratosis laryngis which progressed to malignancy, is presented in serial fashion, correlating the clinical and histopathological findings, with the therapeutic measures employed.

REFERENCES

1. JACKSON, C. AND JACKSON, C. L.: Diseases of the Nose, Throat and Ear., W. B. Saunders Co., Phila., p. 592, 1945.
2. CLERF, L. H.: *J. A. M. A.*, **132:** 823, 1946.
3. LEDERER, F. L.: Diseases of the Ear, Nose and Throat, F. A. Davis Co., Phila., p. 702, 1946.
4. GRAHAM, H. B.: *Arch. Otolaryng.*, **36:** 735, 1942.
5. NEW, G. AND ERICH, J. B.: *Tr. Sect. Laryng., Otol. & Rhin.*, p. 17, 1938.

I like a bit of a mongrel myself, whether it's a man or a dog; they're the best for every day.—George Bernard Shaw *(Misalliance)*.

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INVASIVE HYDATIDIFORM MOLE

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ACCORDING to DeLee, hydatidiform mole occurs in one in 2,000 pregnancies. Greenhill states that 4% of pregnancies which result in spontaneous abortions are hydatid moles and are unrecognized as such. In the Boston-Lying-In Hospital, from January 1932 to January 1942, there were 14 cases of hydatidiform mole, which ran about one in 2,051.

The three cases which will be described were gathered from a total of over 4,000 confinements, from 1935 to 1948, and it is probably unique that all three cases occurred within a few months of each other in the latter part of 1947 and early part of 1948, and that we have had no case prior to this time or since.

The etiology of hydatidiform mole is unknown. It is a cystic degeneration of the chorionic villi. Grossly, the mole resembles a bunch of grapes, varied in size, from a pinhead to a hen's egg. In practically all cases there was no sign of a fetus, although in a twin or multiple pregnancy, a fully developed fetus may be found. Matthieu reported three cases in which a fetus occurred. DeLee and Greenhill state that 2% of hydatidiform moles develop into chorioepitheliomas and that 50% of chorioepitheliomas are derived from the hydatidiform moles. DeLee states that hydatidiform moles occur more frequently in multipara aged over 35 years.

The diagnostic pointers in these moles may be summed up as follows: (1) Irregular vaginal bleeding. (2) Fulminating onset of toxic states. (3) Enlargement of uterus, disproportionate to the number of months of pregnancy. (4) The passage of vesicular material from the vagina. (As will be noted in one case described, the diagnosis was made when the patient passed some typical vesicular material.) In the other two cases, the diagnosis was made because of the unduly great enlargement of the uterus, out of all proportion to the stated number of months of pregnancy.

Careful studies of pathology may give us accurate information on the malignant potentialities of these tumours. The Aschheim Zondek test is of value in eliminating the possibility of chorioepithelioma, because the test usually becomes negative after ten days and if it persists it can indicate either that a piece of the mole still exists or that malignant changes have taken place.

Hertig and Sheldon in their excellent paper, attempted to show correlation between the histologic appearance of the hydatidiform mole and the subsequent clinical course of the patient with respect to the development of chorionic malignancy, and they were able to evaluate malignant potentialities of a mole much more accurately. In their grading of these potentially malignant tumours, two general histologic principles were kept in mind: (1) the degree to which the trophoblast resembled or differed from that of the normal placental tissue in the first trimester of pregnancy and (2) the absolute degree to which it appears to be undifferentiated, using the criteria employed in grading any tumour. Comparison in the first trimester trophoblast was used as a criterion, since it is from pathologic chorion of this developmental age that hydatidiform moles arise.

They found that the more malignant the mole, the more its trophoblast resembled the differentiating trophoblast of the early human ovum during its first week after implantation.

"It is evident from a study of placental development and growth that a tumour derived from trophoblast differs from any other tumour in two respects, (1) it is derived from structures that are not an integral part of the host, and (2) its benign prototype is normally invasive, opens and permeates blood vessels, and thereby often metastasizes to the lungs.

"Because of the first fundamental difference, namely, the tumour host relationship, it is theoretically possible that no matter how malignant a hole appears microscopically, any particular area of trophoblast may not have been in juxta-position to the uterine wall, and hence could not have invaded it. . . . The second fundamental difference, namely the semimalignant attributes of all trophoblast, makes it clear that, since most pregnant patients have trophoblastic metastases, but rarely die from chorionepithelioma, there must be some factor other than its pure morphologic appearance which allows one metastasis to persist and kill the patient while the other disappears. The lytic substance postulated by Fraenkel is possibly the explanation for this phenomenon."

In the 200 cases which Gertug and Sheldon studied, they were able to establish classification on a histologic basis as follows:

1. *Benign hydatidiform moles:* showing none to slight hyperplasia of the trophoblast.
2. *Probable benign hydatidiform moles,* showing slight to moderate hyperplasia of the trophoblast.
3. *Possible benign hyperplasia with slight anaplasia.*
4. *Possible malignant hydatidiform moles,* variable hyperplasia and moderate anaplasia of trophoblast.
5. *Probable malignant hydatidiform moles,* marked anaplasia of trophoblast.
6. *Malignant hydatidiform moles,* marked anaplasia of trophoblast, (exuberant hyperplasia), and often evidence of endometrium invasion.

Chronic malignancies: (1) Chorionepithelioma. (2) Syncytial endometritis. (3) Chorioadenoma destruens and (4) Chorioncarcinoma.

The three cases herewith concerned, from the gross and microscopic appearance, would come under the classification of chorioadenoma destruens and "this is the designation used to cover the group of chorionic malignancies which are characterized pathologically by persistent invasion of the myometrium by low-grade malignant trophoblast, usually attached to its parent-villus. These tumours rarely, if ever, give rise to clinical evidence of metastases, and therefore the prognosis is excellent providing the uterus is removed. This group is characterized clinically by variable amounts of uterine subinvolution, post-molar vaginal bleeding and usually a persistently positive test for chorionic gonadotrophic hormone."

The only serious, though rare, complication of this type is perforation of the uterus, with its resultant sepsis and hæmorrhage and except for this complication, it has been shown that following hysterectomy one can be assured of an almost 100% cure.

Hertig feels that "conservatism should be used in treatment of these cases so that many uteri that might be needlessly sacrificed, would be spared". In only one of the 32 cases he referred to was the uterus removed solely because of a persistently positive Friedman test. Since the test for chorionic gonadotrophic hormone may remain positive for as long as 16 weeks following the expulsion of the benign mole, the average being three months, with variations of 6 days to 10 months according to Pyane, it is obvious that it is of little help in diagnosing chorionadenoma destruens. However, post-molar vaginal bleeding and sub-involution of the uterus are almost invariably present and indicate the need for at least a uterine curettage, with the probability of the subsequent hysterectomy.

The probability that none of the chorioadenomata destruens is subject to metastases appears to be of clinical significance, since this group can be benefited by proper therapy (hysterectomy). Therefore it behooves the clinician to be on the watch for evidence of that condition.

CASE 1

White female, age 32. Past history, non-contributory. Had one child, age 2 years. Patient had three months' amenorrhœa and suddenly began to spot. She was admitted to hospital, examination revealed a uterus about the size of 5 to 6 month pregnancy, soft and spongy on palpation. There were no fetal heart sounds and x-rays of the pelvis did not reveal any fetal skeleton.

Shortly after admission the patient went into labour and passed a profuse amount of vesicles. The uterus contracted down to the size of a two-months' pregnancy and about 7 days after admission she was discharged in good health and no bleeding *per vaginam*. An x-ray of the chest taken prior to dismissal did not reveal any disease. A follow-up showed a definite sub-involution of the uterus and some persistent bleeding.

She was admitted to hospital a month later and a diagnostic curettage was done. Pathological report did not reveal any evidence of malignancy. In spite of this the patient continued to bleed and it was felt advisable to recommend hysterectomy. Finally, two months after the original expulsion of the mole, a total hysterectomy was performed and the following is the pathologists report:

The gross examination reveals a body of uterus showing a marked adenomatous polyposis of the endometrium and what looks like the remnants of a hydatidiform mole. The ovary shows one plum- and one cherry-sized simple follicular cyst containing straw-coloured fluid.

Histological examination reveals some chorionic villi superficially with Langhans and syncytial cells but the latter cells are also invading the superficial and relatively deep sinusoids in the uterine wall. However, there has been no infiltration into the muscle nor are there mitotic figures in the Langhans cells seen. It presents a difficult problem in diagnosis but seems to me to belong to the invasive mole or chorio-adenoma destruens class rather than a true choriocarcinoma.

CASE 2

White female, age 46. Patient had amenorrhœa for four months and because she felt that she was near the menopause, did not deem it necessary to consult the doctor, but when she noticed that her abdomen was reaching large proportions and also because of some spotting, we were consulted and found her abdomen to be the size of a 6 month pregnancy. She was admitted to hospital and x-ray of chest and pelvis were taken: there were changes in the right lung suggestive of low grade chronic inflammation, but no definite diagnosis was made.

A day after admission she began to bleed and had contractions and expelled a large amount of hydatidiform cysts. Uterus contracted down to practically normal size. Her bleeding at the time was quite profuse and required supportive treatment by blood transfusions. She was discharged but continued to bleed for almost two months and on examination of the uterus, it was found to be sub-involuted and large, and hysterectomy was advised. Panhysterectomy was performed. The following is the pathological report:

The gross and histological appearances reveal a body and cervix of uterus showing a hydatidiform mole which is involving the inner aspect of the cavity, but there does not appear to be any undue proliferation and infiltration of the Langhans cells, which one would expect if chorio-carcinomatous transformation had taken place. Such a condition, of course, is potentially malignant and the patient should be kept under observation.

CASE 3

White female, age 23. Past history non-contributory. History of amenorrhœa for three months. Prenatal care revealed uterus size of 4 to 5 month pregnancy. X-ray did not reveal any evidence of fetal skeleton. Admitted to hospital and two days after admission began to have crampy pains and bleeding and on the 3rd day expelled an hydatidiform mole. Patient was discharged 10 days after admittance and advised to return for routine check-up. X-ray of chest was negative.

After a lapse of only two weeks patient began to bleed profusely. She was admitted for D. & C. Shortly after her second admission began to bleed again. Examination revealed a large uterus and she was advised hysterectomy. This was carried out successfully. Following is the pathological report:

The gross and histological appearance reveal a large uterus containing a lemon sized necrotic mass, the remains of a hydatidiform mole, with œdematous chorionic

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villi, which has destroyed the whole thickness of the uterine wall almost to the serous coat. There is no proliferation of the Langhan's or syncytial cells and hence I feel that the condition is thus still benign although it has been locally invasive.

These three patients have been followed very carefully since their operations. Their A.Z. tests have been negative on two occasions. The follow-up of x-ray of lungs have been persistently negative and patients are enjoying good health.

The striking thing about these three cases was the similarity in their symptoms and their course; all three came to hysterectomy because of persistent sub-involution, and persistent bleeding. The only dissimilarity was that one was approaching the menopause and one was a multipara, one had but one child and one was childless. The three have no evidence of metastases to the lungs, their A.Z. tests are negative and they have been diagnosed pathologically as belonging to the group of invasive moles without metastases, or chorioadenoma destruens.

BIBLIOGRAPHY

1. HERTIG, A. T. AND SHELDON, W. H.: *Am. J. Obst. & Gynec.*, **53**: 1, 1947.
2. GASTINEAU, C. F. *et al.*: *J. Clin. Endocrinol.*, **9**: 615, 1949.
3. GOHSTAND, L.: *M. J. Australia*, **1**: 434, 1947.
4. PAYNE, F. L.: *Surg., Gynec. & Obst.*, **73**: 8, 1941.
5. MATHIEU, A.: *Surg., Gynec. & Obst.*, **68**: 844, 1939.
6. KRETCHMAR, L. H.: *Marquette M. Rev.*, p. 1, November, 1948.
7. HENNESSY, J. P.: *Am. J. Obst. & Gynec.*, **57**: 779, 1949.

OBSERVATIONS ON THE ORAL ADMINISTRATION OF CORTISONE ACETATE*

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A. G. GORNALL, Ph.D., *Toronto*

CORTISONE ACETATE, initially supplied as a microcrystalline material suspended in saline, was intended for use by intramuscular injection.[1] In this form the hormone was highly insoluble and daily injections of the material resulted in the production of multiple depots in muscle from which absorption was slow and cumulative, the rate depending to a large extent on the size of the crystalline particles.[2] The slow absorption was probably best indicated by the gradual decrease in the circulating eosinophils to a low level over a period of three to four days (Fig. 1), and also by the lapse of a comparable period of time before a distinct clinical effect was obtained. This delay had its disadvantages where a rapid clinical response was desired as, for example, in status asthmaticus, and might account for some of the differences in the results obtained with cortisone as compared with adrenocorticotropic hormone.[3] However, it also had certain advantages. Intramuscular injections could be administered only once daily or even at forty-eight hour intervals, if the dose required was not too large. Furthermore, when treatment was discontinued, the accumulation of multiple depots in muscle ensured a gradual withdrawal from the effects of the hormone. In diseases where symptoms were prone to relapse, this occurred gradually with less psychological trauma to the patient. The full effect of the hormone would sometimes continue for periods up to seven days after cessation of therapy, when symptoms would commence to return. While the injections sometimes were painful and might cause local induration, this was not usually serious and abscess formation was rare.

The demonstration that cortisone was effective when given by mouth[4] greatly facilitated its administration to patients and thus increased its value. In considering the use of any therapeutic agent, simplicity and ease of administration are always important factors, being second

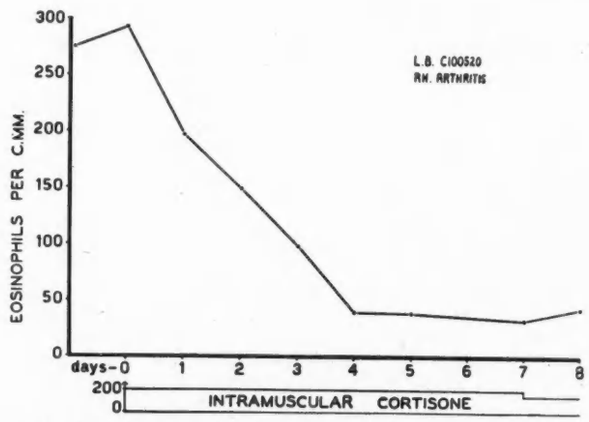

Fig. 1.—Effect on the circulating eosinophils of cortisone acetate administered intramuscularly, in doses of 200 mgm. per day, to a patient with rheumatoid arthritis.

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This study was assisted by grants-in-aid from the Canadian Arthritis and Rheumatism Society.
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only to the effectiveness and reliability of the product. The introduction of cortisone acetate in tablet form appears to have fulfilled these criteria.* In view of the wide application which this material has achieved, it may be of value to record some observations on the administration of this hormone to patients by the gastrointestinal route, both in the suspension and tablet form.

METHOD AND PATIENTS

The results reported herein are based on observations made during the administration of cortisone acetate by mouth, in single test doses, to 55 individuals on 80 occasions (see Table I). The rate of fall of the circulating eosinophils (modified Dunger method[5]) was used as a rough guide as to the rate of absorption of the material. Control eosinophil counts at intervals of one or two hours from 9.00 a.m. to 5.00 p.m. were done on 35 of the patients.

TABLE I.

DISEASE STATES IN WHICH EOSINOPHIL COUNTS WERE MADE FOLLOWING VARYING SINGLE DOSES OF ORAL CORTISONE

Rheumatoid arthritis	18	cases
Reiter's syndrome	2	"
Psoriatic arthritis	1	"
Shoulder-hand syndrome	1	"
Collagen diseases	3	"
Skin disorders	3	"
Pernicious anæmia	4	"
Jaundice, obstructive	2	"
Ulcerative colitis	2	"
Steatorrhœa	1	"
Trichinosis	1	"
Asthma	1	"
Myeloid metaplasia	1	"
Obscure illness (eosinophilia)	1	"
Eosinophilic leukæmia	1	"
Gastrectomy	4	"
Addison's disease	3	"
Normal controls	6	"
Total	55	"

The level of the circulating eosinophils is subject to wide variations in different individuals and in any particular individual at different periods throughout the twenty-four hours.[6] A distinct decrease in the eosinophil count may occur in normal individuals, particularly during the early hours of the day, at times amounting to more than 50%. However it is unusual for the count to fall to very low levels, *viz.*, below 50 per c.mm., without some form of stimulation, unless the initial count was particularly low. Realizing this limitation, it is felt nevertheless that the rate of fall in the circulating eosinophils serves as a useful guide to the rate of absorption of cortisone administered by mouth.

Attempts are presently under way to correlate these observations with the rate of absorption of the steroid as indicated by measurement of the adrenal corticoids in the serum.[7]

Our observations on the therapeutic effect of oral cortisone in various disease states are based on the prolonged administration of this hormone to a total of 61 patients during 72 separate courses. The group includes patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, acute gouty arthritis, Reiter's syndrome, hand-shoulder syndrome, pulmonary fibrosis, asthma, exfoliative dermatitis, chronic urticaria, disseminated lupus erythematosus, periarteritis nodosa and scleroderma. No attempt will be made here to assess the therapeutic value of the hormone in any particular disease state, since this will be the subject of subsequent reports.

OBSERVATIONS

The administration of cortisone acetate orally is followed within a matter of a few hours by a prompt decrease in the number of circulating eosinophils in the peripheral blood (Fig. 2). This drop can be demonstrated with doses as small as 25 mgm., whether administered in the tablet or suspension form. Single doses of 25 and 50 mgm. produced an average eosinophil drop of 71 and 76% respectively (Fig. 3), the maximum decrease occurring in four to five hours and being maintained at a low level for three to four hours. Doses of 100 and 200 mgm. produced only a slightly greater decrease in the eosinophil count, averaging 80% and 92% respectively. The rate of fall was approximately the same, but the count was maintained at a low level for two to three hours longer than with the smaller doses. The rapidity of the response in these tests was comparable to that obtained with adrenocorticotropic hormone. Patients with very high eosinophil counts, over 400 per c.mm., showed a proportionally poorer response.

On six occasions a decrease of less than 50% was obtained. One patient with Addison's disease showed a decrease of less than 50% following 25 mgm. of cortisone; one patient with eosinophilic leukæmia (eosinophil count/20,300 c.mm.) and a patient with an obscure fatal illness (eosinophil count/1,900 c.mm.) failed to obtain a satisfactory

*The cortisone acetate (Cortone-Merck) used in this study was supplied in part by the National Research Council, Canada, and in part by Merck and Co., Inc., Rahway, N.J.

decrease following 50 mgm. of cortisone; one patient with myelosclerosis and myeloid metaplasia (eosinophil count/446 c.mm.) failed to show a significant drop with 100 mgm. of cortisone orally, or on repeated trials with 25 mgm. of adrenocorticotropic hormone intramuscularly; a fifth patient failed to show a significant drop with 50 mgm. of cortisone in tablet form on one occasion, but demonstrated a satisfactory response on subsequent occasions; one patient with a gastrectomy did not respond to 100 mgm. of cortisone in tablet form but demonstrated a satisfactory drop with 100 mgm. of the suspension. With these exceptions a satisfactory response was obtained in the remainder of the trials. Absorption appeared to be delayed slightly when the material was administered immediately after meals but, otherwise, the effect produced was the same.

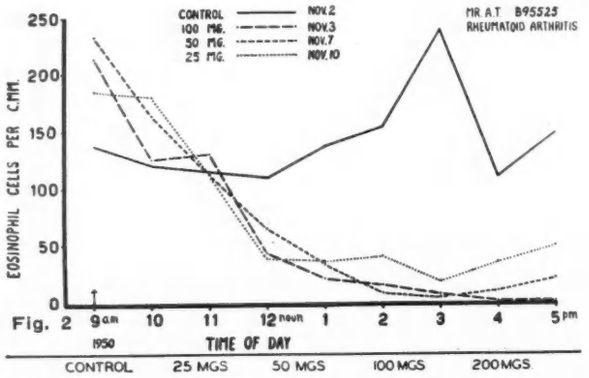

Fig. 2

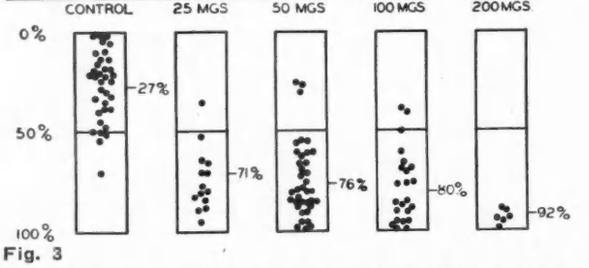

Fig. 3

Fig. 2.—Effect on the circulating eosinophils of cortisone acetate administered orally in varying doses to a patient with rheumatoid arthritis. **Fig. 3.**—Percentage decrease in the circulating eosinophils between the hours of 9.00 a.m. and 5.00 p.m. in 35 controls and in 80 patients following varying doses of cortisone acetate administered orally. Each dot represents one patient.

In one patient 25 and 50 mgm. of cortisone dissolved in 10 c.c. of 95% ethyl alcohol and given intravenously in 500 c.c. of normal saline over a four-hour period did not produce any greater response than the same preparation given by mouth. In another patient, cortisone acetate suspension deposited by means of a Harris tube into the stomach, duodenum and ileum produced a good response on all occasions (Fig. 4). Likewise, placing the suspension in the distal loop of a transverse colostomy in a patient with ulcerative colitis produced a good eosinophil suppression.

Preliminary studies on the estimation of adrenal corticoids in serum suggests that the absorption of cortisone from the gastrointestinal tract is more rapid than the drop in the eosinophil count would indicate, probably reaching a maximum level as early as two hours after administration of the dose and dropping off rapidly within the next two hours.[7] The fall in the eosinophil count lags by some two to three hours.

In the group of patients receiving prolonged courses, no instance of gastrointestinal irritation or intolerance to the hormone was encountered. Fifteen of the patients had previously received cortisone by injection and all expressed a preference for the oral form. Patients suffering from diseases which were favourably affected uni-

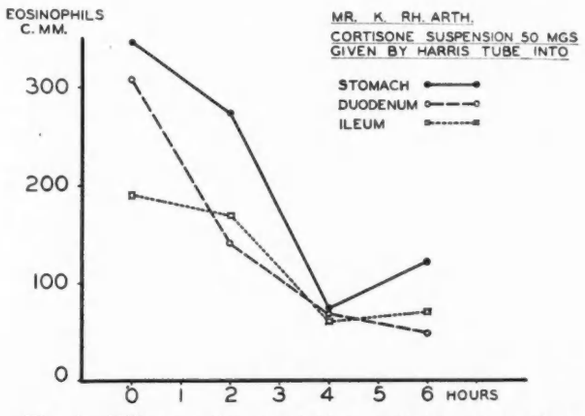

Fig. 4.—Effect on the circulating eosinphils of cortisone acetate deposited in the stomach, duodenum and lower ileum in a case of rheumatoid arthritis.

formly showed a more rapid response with oral cortisone than was observed with the injectable material, and equalled the rapidity of the response obtained with adrenocorticotropic hormone. A subjective change was usually noted by the patient within six to twelve hours. In a similar manner, return of symptoms in disease states which showed a tendency to relapse occurred more rapidly, and sometimes dramatically so, although this could be minimized by tapering the dose over a period of days or weeks. Qualitatively the clinical improvement observed was in no way different from that obtained with injectable cortisone.[8] Physiological and hormonal effects such as salt retention, effect on carbohydrate and nitrogen metabolism, stimulation of appetite, euphoria and the physical manifestations of hyperadrenalism seen during prolonged

administrations were comparable regardless of the route. Complications such as transient psychosis, spontaneous fractures of bone, perforation or bleeding from a peptic ulcer and coronary occlusion have been encountered regardless of how the hormone has been given. No serious suppression of adrenal cortical activity occurred in this group, although several patients had received oral cortisone continuously for as long as nine months.

Comparison of the effectiveness of oral and injectable cortisone on a quantitative basis is difficult owing to the long period of time necessary to establish a minimum maintenance dose. This is particularly true of intramuscular injections. Experience would indicate, however, that the daily requirement is about 10 to 25% greater when the hormone is given by the oral route,[9] but it approaches more closely the intramuscular requirement when it is given in multiple small doses spaced regularly throughout the twenty-four hours. Making use of criteria such as the clinical course, sedimentation rate and temperature response it has been possible to show that, with prolonged administration, equivalent doses given intramuscularly have been somewhat more effective. Patients who have shown reactivation of their disease on a maintenance dose orally have often been brought under control again with the same dosage schedule given intramuscularly (see Fig. 5).

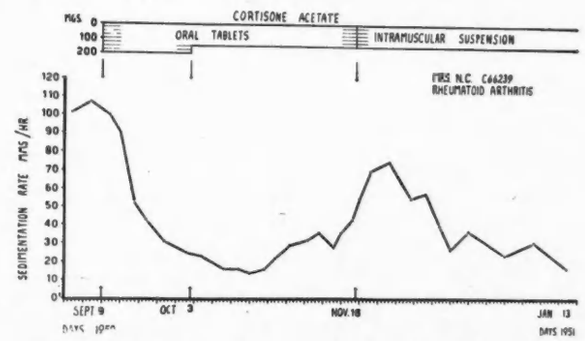

Fig. 5.—Effect of cortisone acetate on the sedimentation rate in a patient with rheumatoid arthritis. A good response was obtained with doses of 200 mgm. orally, but relapse occurred when this was reduced to 150 mgm. per day. A change to intramuscular injections, in the same doses, effected further remission.

An abrupt change from oral to intramuscular administration may be followed by a temporary relapse of symptoms, due to the rapid loss of effectiveness of the oral hormone and the delayed effect of the intramuscular hormone. In any change-over from oral to intramuscular administration, the two methods should be overlapped by twenty-four to forty-eight hours. When changing from intramuscular to oral administration this is not necessary, since the effect of oral administration is very rapid and material continues to be absorbed from the depots in muscle for several days.

Conclusions

Cortisone acetate is rapidly absorbed from the gastro-intestinal tract. It is well tolerated whether given by tablet or in the suspension form, but there may be a lingering bitter taste with the latter preparation. Patients universally express a preference for the oral route. The absorption of a single dose reaches its maximum within a few hours and, in doses of 25 and 50 mgm., appears to exert its full effect for somewhat less than six hours. In order to obtain the optimum effect of the hormone orally, therefore, doses should be administered at intervals of not longer than six hours. Satisfactory clinical responses may be achieved with longer intervals, but it is probable that the longer spacing between doses is more wasteful and will necessitate a larger dose to achieve the same result. While the requirement in any given patient may be slightly greater when it is given by mouth, the clinical and physiological effects of the hormone are otherwise the same. With oral medication a subjective response was often noted within six to twelve hours of the initial dose and compared favourably with the speed of action of adrenocorticotropic hormone given intramuscularly or intravenously. Similarly, abrupt withdrawal of the hormone following oral administration is likely to be followed by a more rapid relapse of symptoms than would occur after intramuscular injection, and may occasionally be very abrupt. Whether the medication is taken before or after meals appears to make no significant difference to the ultimate therapeutic result.

Since this paper was submitted for publication the subject has been presented in a paper by Thorn *et al.*,[10] with similar conclusions.

References

1. Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F.: *Proc. Staff Meet., Mayo Clin.*, **24**: 181, 1949.
2. Kendall, E. C.: *Proc. Staff Meet., Mayo Clin.*, **24**: 298, 1949.
3. Randolph, T. G. and Rollins, J. P.: *J. Allergy*, **21**: 260, 1950.
4. Freyberg, R. H., Traeger, C. T., Adams, C. H., Kuscu, T., Wainerdi, H. and Bonomo, I.: *Science*, **112**: 429, 1950.
5. Dunger, R.: *München. med. Wchnschr.*, **57**: 1910, 1942.
6. Rud, F.: The Eosinophil Count in Health and in Mental Disease; A Biometric Study, Johan Grundt Tanum Forlag, Oslo, pp. 178, 199 and 216, 1947.
7. Gornall, A. G. and Ogryzlo, M. A.: Personal observations.
8. Ogryzlo, M. A. and Graham, W.: *J. A. M. A.*, **144**: 1239, 1950.
9. Boland, E. W. and Headley, N. E.: *J. A. M. A.*, **145**: 8, 1951.
10. Thorn, G. W. *et al.*: *New England J. Med.*, **245**: 549, 1951.

RÉSUMÉ

L'absorption de l'acétate de cortisone se fait rapidement par le tractus gastro-intestinal. Sous forme de comprimé il est bien toléré, mais en suspension il laisse un goût amer. Les malades paraissent tous en faveur de la voie orale. L'effet maximum se manifeste en moins de six heures, à la dose de 25 à 50 mgm, c'est pourquoi on en obtient le meilleur rendement à cet intervalle. A des doses plus éloignées il semble que pour obtenir un résultat satisfaisant il faille de plus fortes doses et le traitement en coûte davantage.

Si l'on compare les résultats obtenus par la voie orale, on note de dons effets de six à douze heures après la prise du médicament, et cette rapidité d'action se compare favorablement avec celle de l'injection intraveineuse ou intramusculaire du produit. Dans un même ordre de faits, dans le cas de cessation abrupte de la drogue par voie orale on note une reprise plus rapide des symptômes que celle qui est observée après injection intramusculaire.

Il semble importer peu au point de vue de résultat thérapeutique ultime que la médication soit prise avant ou après les repas. Enfin, si l'on change brusquement de la voie orale à la voie intramusculaire, il peut arriver que les symptômes réapparaissent temporairement, cela étant dû à la fois à la perte rapide de l'efficacité de l'hormone orale et à l'effet retardé de l'hormone intramusculaire.

PREVENTION IN THE CONTROL OF GLAUCOMA

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PUBLIC INTEREST in the control of blindness has not been manifested to nearly the same extent as in the cases of other scourges such as tuberculosis, syphilis and cancer. However, in recent years, judging by published articles and the adoption of various preventive methods, it is evident that more active measures for the prevention of blindness are being taken in all countries of the world.

At the last Congress of the International Association for the Prevention of Blindness held in London in July, 1950, the main topic was the classification of the causes of blindness. This has revealed the most frequent causes of blindness in different countries. There are some countries in which certain eye diseases are predominant, such as trachoma in Egypt. But, what is most noticeable in all countries is the universal frequency of glaucoma as the cause of blindness.

In Canada as in the U.S.A. about one person in eight hundred is affected with blindness. Glaucoma alone is responsible for 15% of this blindness. It is one of the most disconcerting and serious eye diseases known.

TABLE I.

CAUSES OF BLINDNESS IN CANADA IN PERCENTAGES

Indefinite causes	18.7
Cataract	18.2
Infectious diseases	15.6
Glaucoma	15.0
Prior to birth	14.5
Traumatism	7.5
General disease	6.1
Others	3.0
Tumours	1.0
Intoxications	0.5

Glaucoma was formerly defined as "a disease of the ocular globe clinically characterized by the increase in tension". But today we know that this definition is not accurate. It is more clinically correct to say that the disease is usually characterized by three cardinal symptoms; ocular hypertension, alteration in the vision and excavation of the optic disc. Of these three symptoms the most constant is the elevation of the ocular tension. However, one must not confuse ocular hypertension with glaucoma as these terms are not synonymous. For instance, every day we find cases of glaucoma without hypertension. We also find cases of increased tension accompanied by marked alterations of the visual field without showing the slightest excavation of the optic disc. Finally, we have noticed cases with long standing hypertension and marked excavation of the optic disc which had never shown any alteration of the visual field. These monosymptomatic or incomplete glaucoma probably are at the time they are discovered in an intermediary stage which is a forerunner of the typical state of glaucoma.

Glaucoma may occur in several clinical forms, the most frequent being (1) the congestive form and (2) simple chronic glaucoma. It is not suitable in an article such as this to describe all clinical forms and aspects of this disease. Moreover, it is difficult in most cases to draw a dividing line between these various forms. A case of simple glaucoma may easily turn into a congestive glaucoma and vice versa. We shall only give here a detailed description of the most common and most disastrous form — chronic simple glaucoma.

Symptomatology.—Chronic simple glaucoma is insidious in its onset and the early diagnosis requires both many and careful examinations. This disease involves either one or both eyes, develops very slowly and may progress for a

long time before the patient complains or before a diagnosis is made. No external signs draw attention to the eye. The cornea and the transparent media appear normal. The pupil may be of normal size or slightly dilated. The tension may appear normal on palpation. A somewhat elevated tension may be revealed by the tonometer. Sometimes the hypertension may only be detected after repeated examinations with the tonometer or by various tests on different days. The central visual acuity is generally normal.

Certain minor subjective phenomena sometimes presented by the patient should attract our attention. They are temporary fogginess of the vision, a decrease of accommodation or premature presbyopia and especially the seeing of coloured rings around lights. The careful exploration of the visual field will give valuable information. At the very outset there is an increase of the normal central scotoma, a prolongation of the blind spot upward or downward. This early evidence, called "the sign of Seidel" should be sought with the help of the tangent screen. The perimetric examination finally shows a progressive narrowing of the visual field especially on the nasal side.

The ophthalmoscopic examination shows alterations of the optic disc and retinal vessels. A more or less pronounced pallor and excavation of the optic disc is generally noted. The pallor is a sign of atrophy following the destruction of the nerve fibres. The excavation is probably due to two factors, pressure and atrophy. The state of the retinal vessels indicates sclerosis and difficult blood circulation. The capacity of the arteries is generally decreased; the veins are congested, twisted and dark, showing venous stasis. A venous pulsation is frequently noted at the level of the optic disc. This is not a sign of venous hypertension, but it shows that the blood pressure is equal to the intra-ocular tension. Now when the tension is increased it means that the venous pressure is also increased. An arterial pulse which is infrequently observed is a sure sign of ocular hypertension. The examination of the irido-corneal angle (gonioscopy) gives information on the depth of the angle and permits us to note localized adhesions or total synechiæ.

Development.—Glaucoma is a condition which tends to become aggravated and leads to blindness. Without treatment the patient becomes blind. If treated the final results depend on two factors: how far the disease has progressed at the time of diagnosis and the adequacy of the treatment subsequently given. The prognosis should always be guarded.

Pathogenesis.—There are at the present time two conflicting theories to explain the causative mechanism of glaucoma. One is purely mechanical and states the cause as an obstacle to the flow of the aqueous humour; the other is more physiopathological and attributes the origin of the disease to neuro-vascular disturbances.

Mechanical theory. — The followers of this theory base their belief upon anatomical considerations. In other words, the disease is caused by an obstruction of the flow of the aqueous humour in the filtration angle. This is the retention theory and depending on whether the irido-corneal angle is widely open or quite closed when the first evidence of the disease appears either simple glaucoma or congestive glaucoma develops. This theory is based upon the study of the filtration angle (gonioscopy). In fact, gonioscopic examinations show that congestive glaucoma generally occurs in eyes having narrow or closed filtration angles whereas the angle is usually normal in chronic glaucoma. The numerous proponents of this mechanical theory in the United States have adopted a new classification for the disease—wide angle glaucoma and narrow angle glaucoma.

Neuro-vascular theory.—According to Duke-Elder, glaucoma would be attributable to a vascular disturbance. In the congestive forms, this disturbance is revealed by vasodilatation, capillary hyper-permeability, stasis and œdema. The congestion and œdema of the ciliary body bring the iris close to the cornea thus obstructing the drainage channel. In chronic simple glaucoma, the vascular disturbance exists in the form of capillary sclerosis rather than stasis. With this pathogenesis, Duke-Elder seems to solve several cases frequently encountered clinically, namely cases of glaucoma without tension. If, in fact, the capillary sclerosis is more pronounced in the posterior part of the globe, we find changes in the visual field and excavation in the optic disc, without intraocular hypertension. If, on the contrary, the anterior part of the globe is primarily affected, the tension increases at first, because the irido-corneal angle is involved. In such a case, there is no early excavation of the optic disc nor any scotoma in the visual field.

L. Weepers, in his contribution to the study of simple glaucoma, draws attention to the importance of vascular lesions in this affection.

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These vascular lesions, he says, determine the symptomatology of the disease: "the lesions of the vessels of the anterior uvea produce the change in the tension; the vascular retinal lesions cause the visual losses; the vascular lesions of the head of the optic nerve cause the papillary excavation".

This conception that glaucoma is a vascular disease is not new. In 1929, Magitot blamed a disturbance of the venous circulation. "In Glaucoma", he said, "the vascular pressure has the following characteristics; moderate increase of the arterial tension, but sometimes considerable increase of the venous pressure". Bailliart shows that the choroidal vessels are always sclerotic, even during the pre-glaucoma period. Cictolo studied the blood pressure by Claude's method, and noted that the pressure was always increased in persons suffering from glaucoma. In the author's opinion, a normal venous pressure is more important than a normal arterial one. If the small arteries are hardened, the ocular tension may be normal, but if the veins are sclerotic, the ocular tension increases.

Treatment.—It is universally recognized that glaucoma is not in itself a disease of the eye, but a local manifestation of a constitutional trouble. The glaucomatous eye is a sick organ, but only as a part of a sick body. Although this is admitted, it appears that the ophthalmologist does not carry out his clinical examination beyond the visual organ. He forgets too readily the general constitutional deficiencies and limits himself purely to local treatment. Glaucoma develops in a particular environment characterized by a vascular and neuropathic condition. The vascular changes noted in cases of glaucoma involve all the vessels of the body. The arterial and venous pressures should be taken. They are generally abnormal. The arterial tension is seldom much elevated, but, the venous pressure is always above normal.

This disease is related to a disturbance of the nervous system. A person suffering from glaucoma is irritable, emotional, anxious. It is necessary then to look for the presence of factors which are possibly responsible for the nervous upset. A good examination of endocrine function is required. The hereditary factor should always be suspected, as it often appears as an underlying cause. It is obvious that deficiencies in general hygiene should be corrected. In this respect, muscular exercises have good effects in reducing the intra-ocular tension.

The family physician should not prescribe medication containing belladonna, atropine and other mydriatics to a patient suffering from or predisposed to glaucoma, without first consulting the ophthalmologist. The physician should also remember that the prolonged use of belladonna and its derivatives may hasten an attack of glaucoma.

The topical treatment consists in the use of myotic alkaloids, to decrease the tension. There are many such myotics and they may be used according to the patient's tolerance. To the classical remedies pilocarpine and eserine may now be added a long list of myotics including mecholyl, doryl, furmethide, carcholin, prostigmine, adrenalin, floropryl. Pilocarpine is still the least irritating substance and the one used most frequently. The number and time of instillations should be strictly explained and defined.

Surgical treatment is used when the hypertension is constant or when there is narrowing of the peripheral visual field. The object of the operation is to create a sub-conjunctival or suprachoroidal fistula. In France, the procedure is called the Lagrange's operation, in England Elliott's, in Germany Heine's cyclodialysis, in Scandinavia Holt's iridencleisis. At the present time, ophthalmologists seem to favour the latter procedure.

GLAUCOMA CLINIC AT THE ST. SACREMENT HOSPITAL

The Glaucoma Clinic at the St. Sacrement Hospital, the second to be opened in Canada, was established through federal-provincial agreements to promote public health. It results from an active co-operation between the University Authorities and the Provincial Department of Health. It is a milestone in the overall plan conceived by the Division of Blindness Control of the Department of National Health and Welfare, at Ottawa. This plan is designed to put into operation several organizations of this kind in Canada, and we can expect to see them in Quebec and in the main rural centres.

The object of these clinics is to detect and diagnose as early as possible all cases suspected of or suffering from glaucoma. Too often when confronted by a patient whose glaucoma has progressed to such an extent that the diagnosis is clear, the ophthalmologist is unable to do anything worthwhile about it. Primarily prevention centres, these clinics quickly became a fertile source of observation and research. Because of these Clinics all aspects and treatment of the disease can be studied.

ACTIVITIES OF THE ANTI-GLAUCOMA CLINIC AT THE ST. SACREMENT HOSPITAL FROM APRIL 1, 1950 TO FEBRUARY 1, 1951

Our Glaucoma Prevention Clinic has been in operation since April, 1950. By February 1, 1951, 111 patients have come for consultation, involving 809 examinations during that period. 103 of these patients were recognized as being pre-glaucoma or glaucoma cases. These figures plainly show the necessity for such a Clinic as well as the large number of patients who have the disease. It is open to all classes of patients who without charge receive the benefit of all modern techniques designed to detect and where applicable make an early diagnosis of the disease.

The following tables, although necessarily incomplete, are self-explanatory.

TABLE II.

PATIENTS ADMITTED	
From the city	55
From outside	56
Total	111

TABLE III.

SEX DISTRIBUTION	
Male	38
Female	73

The average age of the patients admitted was 48 years. We believe as the years go on that this average age will be found to be lower because when this Clinic is better known, it will attract a larger number of patients who will be examined earlier and therefore at a younger age. Twenty patients were hospitalized.

TABLE IV.

EXAMINATIONS	
Hospitalized patients	399
Outpatients	410
Total	809
Average number of examinations per patient	7

We believe that the average age of glaucoma is 60 years. The remark respecting the average age of patients admitted applies here.

The number of pre-glaucoma cases was 36, the average age being 30 years.

TABLE V.

DIAGNOSES TRUE GLAUCOMA	
Absolute	7
Acute	3
Chronic congestive	3
Chronic non-congestive	48
Secondary	8
Total	69

TABLE VI.

PATIENTS OPERATED ON	
Filtrating operations	11
Evisceration	1
PROGRESS OF THE CASES	
Improved	39
Stationary	54
Progressive aggravation	10

SUMMARY

1. Glaucoma is a frequent cause of blindness.

2. The result of the treatment depends on its early application and the early detection of the pre-glaucoma condition.

3. This detection will be made through thorough examination of the patients since the methodical and careful examination of the fundus of the eye may reveal cases not yet apparent.

4. As the mechanical explanation of the pathogenesis of glaucoma seems to be falling into discredit, it is important to carry out our investigations beyond the visual system. Moreover, this disease is first of all characterized by a vascular deficiency and a nervous imbalance.

5. The organization of a glaucoma clinic seems to be the best means of meeting the requirements of these patients who need repeated and careful examinations.

6. This preliminary report on the activities of the clinic shows that such clinics which will be set up throughout the country for the study and detection of glaucoma will be most useful in controlling this disease. However, the co-operation of all physicians, both general practitioners and specialists is required and absolutely necessary.

BIBLIOGRAPHY

1. MEYER, S. J.: Incomplete Glaucoma, *Eye, Ear, Nose & Throat Monthly*, September, 1950.
2. MAGITOT, A.: *Ann. d'ocul.*, **180**: 1, 1947.
3. DUKE-ELDER, S.: *Am. J. Ophth.*, **33**: 1, 1950.
4. SCHEIE, H.: *Arch. Ophth.*, December, 1950.
5. DUKE-ELDER, S.: Textbook of Ophthalmology, Vol. 3, p. 3389.

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THE EOSINOPHIL LEVEL IN PSYCHIATRIC CONDITIONS*

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IN RECENT YEARS considerable interest has been aroused in the measurement of adrenocortical function. Of the eight or more indices of adrenocortical activity, one test—the measurement of the level of circulating eosinophils—lends itself most readily to easy and routine clinical usage. Possibly the most sensitive indicator of adrenocortical activity, and certainly the most readily available test for the clinician, it has been criticized by some workers because of its great variability. However, it is just this very sensitivity that makes this test of considerable interest to psychiatrists, since it may offer an objective assessment of the patient's emotional state or his reaction to environmental or internal stress.

It is essentially a clinical test, and should perhaps be viewed within the same frame of reference as such phenomena as the pulse rate, blood pressure, white blood count, etc., all of which are clinical tests, all commonly used, and all susceptible to modification by psychological mechanisms.

This report is concerned with our investigations and findings in the following areas: (1) Diurnal variation of eosinophil count and its significance. (2) Attempts to establish "ranges" of average eosinophil levels and to establish a correlation between these ranges and psychiatric conditions. (3) The effects of certain specific treatments and procedures on the eosinophil count.

Two important factors are to be considered in the evaluation of eosinophil counts: first, the possibility of errors in technique, and second, the not inconsiderable variation seen in normal subjects throughout the day, and perhaps even from minute to minute.

For our counts a solution of 0.1% phloxine in propylene-glycol, 50 c.c. and distilled water, 50 c.c. was used as diluent and stain. Blood samples were taken from the finger-tip and drawn up into a 1/10 dilution in a standard white blood cell pipette. One hour was allowed for complete staining, and a Fuchs-Rosenthal counting chamber, capacity 3.2 c.mm. was employed. Double counts were done in many cases, and where possible, counts were checked by two workers independently. It has been recommended that these measures give the maximum technical accuracy possible for this test.[1]

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The most complete evaluation of the limits of reliability of the eosinophil count yet published has been made by Best and Sampter[2] who, on the basis of a large number of counts, concluded that there is, as in practically all test procedures of this nature, what they term an "intrinsic error". This intrinsic error varies with the number of cells counted, and figures for eosinophil responses which do not exceed this limit of intrinsic error should probably not be used as evidence of a significant variation.

It has been established that stimulation of adrenal-cortical function is followed by eosinopenia.[3] It is, however, not certain that every fall in the eosinophil count is due to a rise in the functional level of the adrenal cortex. Little is known, in fact, about the mechanism which brings about the disappearance of circulating eosinophils. Factors not directly related to the adrenal cortex may produce this effect. Similarly, it is probable that a rise in the eosinophil level is not merely due to suppression of adrenal cortical activity, but that there are factors which are responsible for the release of eosinophils independent of the adrenal cortex, as has been demonstrated for lymphocytes by Elmadjian.[4]

Increases in the eosinophil count tend to differ from observed decreases in two essential aspects: (1) They occur with greater rapidity than the decreases. (2) Percentage changes of considerable extent occur more frequently in the upward than in the downward direction. In our material of longitudinal observations covering periods of several weeks, we found consistently that percentage changes of more than 50% between two consecutive counts occur three to four times as often in the upward as in the downward direction.

It should be stressed at this point that while we are aware of the interdependence of eosinophil level and adrenal cortical function, we are not prepared to interpret every observed change in the eosinophil count and in the clinical condition of the patient as the effect of stimulation or inhibition of the adrenal cortex.

A great deal has been said and printed in recent years about the relation of endocrine functions to emotional conditions. Unfortunately, much of the published material is lacking in diagnostic precision with regard to the psychological observations. Emotional states are remarkably complex phenomena and lend themselves poorly to generalizations unless they are manifestations of well established diagnostic

entities. It has, for instance, been reported by a number of authors that the administration of ACTH or cortisone in some cases produces euphoria or depression. A careful analysis of the emotional deviation is usually not undertaken. There is considerable difference between the euphoria associated with the pathological pressure and drive of the manic patient on the one hand, and the joyful exuberance of the student who has just learned that he passed in the final examinations. These forms of euphoria, both associated with cerebral stimulation, differ considerably in nature from the disinhibited "slap-happiness" of an intoxicated person, or again the serene feeling of intense well being that an individual may experience while wandering through the woods on vacation.

The amount of tension admixed to the spectrum of possible emotional conditions is, in our opinion, the most important single factor in determining the eosinophil level as far as it is dependent on psychological influences.

Since the term "stress" plays such an important rôle in most publications dealing with physiological responses to environmental stimuli, it might be in place here to draw attention to the fact that there is an essential difference between primarily physiological stress and primarily psychological stress. In the case of the former the *awareness* of stress is only incidental and sometimes absent, as, for instance, in the case of the so-called sugar stress. In the case of psychological stress, however, the awareness of a stressful experience is an integral part of the test situation. The degree of emotional tension which may influence adrenal cortical function and the eosinophil count is dependent mainly on the awareness of stress.

DIURNAL VARIATIONS IN EOSINOPHILS

An interesting study of diurnal variation was made by Rud[5] in Norway, who showed:

1. The level of eosinophils fluctuates considerably and rapidly, and the greater the mean count, the greater the degree of fluctuation.
2. The eosinophil levels show a definite diurnal variation which may be masked by short-time fluctuations, but will become evident on averaging many daily curves. Rud found a mid-morning drop of about 20% from the 8 a.m. level, with a return to that level shortly after noon and a rise of about 30% above it in the middle of the night. Slight dips were found to follow meals. Fasting subjects showed a continuous fall extending into the early afternoon.
3. He found that normal individuals maintained within broad limits the same general level of eosinophils over prolonged periods of time, and that this is not altered by menstruation, colds, or season of the year.

One aspect of our own investigation was concerned with the diurnal variation in normal individuals, and our findings would tend to bear out Rud's figures with respect to range of normal variation. Eleven individuals on the hospital staff, of both sexes, of varying ages and occupations, were tested and counts taken at 9.00 a.m., noon and 5.00 p.m. Individual variations ranged from 12.5 eosinophils per c.mm. to 368 per c.mm. in terms of absolute count, and on comparing the levels during the day, it was found that in the course of a day, there were percentage changes in different individuals of from + 158 to –46%.

However, no consistent conformity to the average pattern Rud reported was found, but rather there tended to be three different ones: One pattern showing a gradual fall from a 9.00 a.m. high to a 5.00 p.m. low, another showing a gradual rise from 9.00 a.m. to 5.00 p.m., and finally, a pattern showing a fall at noon-time with a rise at 5.00 p.m.

It is interesting to note in this connection that Pincus,[6] studying 17 ketosteroid excretion from the point of view of diurnal variation, noted a maximal output shortly after waking and a decline thereafter to minimal values at night. He also showed that psychomotor stress caused excretion of increased amounts of 17-ketosteroids and corticoids.

Ranges of eosinophil counts.—One of the objects of this investigation was an attempt to establish ranges of eosinophil counts, both normal and abnormal, in order to allow for the interpretation of pathological findings.

Eosinophil counts were taken on a number of unselected patients recently admitted to a mental hospital and compared with counts done on a group at the time of discharge. Several patients of this discharge group had also been included previously in the admission group. On the basis of thirty cases in each group, it was found that the average count for new admissions was 101.2 per c.mm., and 170.1 per c.mm. for patients ready to be discharged. Noteworthy were the great individual differences which were recorded, *e.g.*, a minimum count of 101.2 and a maximum count of 743 both of which were taken on patients whom we considered clinically recovered.

In view of the great individual fluctuations it seems practical to establish three ranges: (1) Low range—to include counts from 0 to 100. (2) Middle range—from 100 to 250. (3) Upper range

—250 and above. Most cases tend to fall into the middle range, but it should be pointed out that counts in the high range must be scrutinized with regard to allergic conditions and the presence of parasites. We have gained the impression that counts falling into the *low* range would appear to be of greater diagnostic psychiatric significance.

Factors which influence the eosinophil count.—In addition to the physiological and diurnal variations, a number of factors which lower the eosinophil count have been described. Much less is known of factors which cause a rise in eosinophil count, although in general terms, this would, in the absence of allergy and parasitic conditions, tend to be associated with relaxation or exhaustion.

Physiological factors.—ACTH injected in 25 mgm. doses has been found to result normally in a decrease of at least 50% in the eosinophil count, and this is regarded as a standard test of adrenocortical responsivity.[7] Cortisone is also a strong eosinopenic agent and the eosinophil response is similar in extent and direction to that of ACTH but not quite so consistent, due to a later tendency to a rebound effect when the adrenal cortex is suppressed.

Adrenalin and similar drugs would appear to be a most potent stimulus to adrenocortical activity. Eosinopenia of 70 to 80% is reported following injection of 1.5 mgm. adrenaline,[8] while Best and Sampter[2] found 0.2 mgm. of adrenaline consistently resulted in an eosinopenia of 50% or more. They reported also that ephedrine in doses of ¾ grain was as effective as adrenaline in this connection. These changes are not seen in Addison's disease or in hypopituitarism and are diminished in malnutrition. The response to adrenaline or ephedrine might be suggested as a test of adrenocortical reactivity, comparable in effectiveness to the response to injected ACTH.

Hyperglycæmia[9] has been found to create a stress situation to which the individual responds by an increased output of adrenocortical hormone. The lymphocyte response to glucose would seem to be somewhat impaired in schizophrenia according to some investigators.[10] Adequate studies of the eosinophil response to glucose are not available.

Stein *et al.*[11] studied the effect of increased metabolism on the eosinophil response in schizophrenics and other emotionally disturbed subjects and found no essential difference between these and normal subjects, but they did establish that the increased metabolism is in itself a strong eosinopenic agent.

Considering the possibility that age may influence the eosinophil count since it has been shown that there is a relationship between age and adrenal responsivity,[12] we investigated the eosinophil count in a series of patients aged 65 years or over and suffering from senile psychosis. Our results showed average counts well into the upper range in these subjects.

Investigating the effect of electroconvulsive therapy, other workers[13] have reported an early rise in eosinophils occurring ten to fifteen minutes after the convulsion with a later fall some 30 minutes to three hours after the treatment. This fall is later compensated for and original levels regained or surpassed 24 hours after treatment. Altschule[14] has further reported evidence of a diminished eosinophil response when treatments are given closer together, though no correlation was found between this phenomenon and clinical response to electroconvulsive therapy. It has been our impression that the eosinophil response to electroconvulsive therapy is by no means as clear-cut as this, and that the influence of changes in the patient's clinical condition and general tensional level are so great that in each case the effect of electroconvulsive treatment on the eosinophil level should be considered on a strictly individual basis. The possibility of a rise or fall after treatment and a great variability in the length of time for the count to return to pre-treatment values should be steadily kept in mind.

The eosinophil response to insulin was studied in nine schizophrenic patients receiving insulin coma treatment. Dosage of insulin varied between 120 and 500 units. Counts were taken at 7.00 a.m., immediately before the administration of insulin, again at 10.00 a.m., again at 11.00 a.m. (immediately before being awakened by intravenous glucose and oral sucrose) and then again four hours after the termination of coma.

Table I shows an initial range of eosinophil count varying from 125 to 936. A general downward trend from 7.00 a.m. to 11.00 a.m. was noted, the mean percentage drop being 44.6% and the range of percentage drop being from 16 to 77%. The greatest drop in eosinophil level was seen between the 11.00 a.m. and 3.00 p.m. readings, the mean per cent fall being 81.5% and the range being 51 to 90%. The mean percentage fall from the pre-insulin level to the

3.00 p.m. level, is seen to be 89% and the range of this drop to be 84 to 95%.

It was felt that this great drop in eosinophil count between 11.00 a.m. and 3.00 p.m. might actually reflect a "sugar stress", and so in one of these insulin patients the effect of giving simply a heavy oral and intravenous dose of glucose and taking serial eosinophil counts was studied. Conditions were duplicated as nearly as possible to insulin coma treatment and counts were done at the same intervals as before. There was no variation seen in counts during the day until four hours after the ingestion of sugar and the mid-day meal at which time there was a drop of 35% in the eosinophil level as compared with the three initial readings.

Cleghorn and Graham,[16] in concluding that there was no apparent defect of adrenocortical reactivity in psychoneurotics, found that the magnitude of the response to ACTH and to artificial stress situations was influenced by the degree of anxiety experienced by the patient.

A recent study on response to stress in college oarsmen[17] reported consistently low eosinophil counts during the period of great emotional stress and anxious anticipation with high levels during the relaxed after-periods. We have investigated the eosinophil counts of a number of medical students in the tense moments immediately preceding their final examinations and found eosinophil counts in the low range in each case, with a return to counts in the middle or upper ranges 24 hours later. The only exception was seen in an individual who had just suffered an exacerbation of his allergic rhinitis.

TABLE I.

INSULIN SHOCK
EOSINOPHIL RESPONSE TO COMA DOSES OF INSULIN

Case No.	*Ins. units*	*Eosinophils 7.00 a.m.*	*Eosinophils 11.00 a.m.*	*% change 7.00 to 11.00*	*Eosinophils 3.00 p.m.*	*% change 11.00 to 3.00*
1	350	334.0	76.0	– 77.1%	37.0	– 51.3%
2	260	287.5	115.7	– 59.8%	28.0	– 76.0%
3	120	125.0	56.2	– 55.0%	6.2	– 89.0%
4	500	206.0	171.6	– 16.7%	25.0	– 85.5%
5	500	936.1	718.7	– 23.2%	109.4	– 84.9%
6	250	503.1	231.5	– 53.9%	68.7	– 70.4%
7	400	125.0	37.5	– 70.8%	6.3	– 84.0%
8	380	115.5	68.7	– 40.5%	6.5	– 90.5%
9	250	428.0	218.6	– 47.9%	28.1	– 87.0%

Average % change 7.00 a.m. to 11.00 a.m. – 44.6%
Average % change 11.00 a.m. to 3.00 p.m. – 81.5%
Average % change 7.00 a.m. to 3.00 p.m. – 89.6%
Range % change 7.00 a.m. to 11.00 a.m. – 16.7% to – 77.1%
Range % change 11.00 a.m. to 3.00 p.m. – 70.4% to – 90.5%

The response to 40 units of insulin under the so-called "modified insulin" routine was also studied. Five patients were selected. Counts were made before insulin, two hours after insulin and two hours after ingestion of sucrose. A fall in eosinophils occurred in each case. This was most pronounced two hours after the termination of the hypoglycæmic state, but the percentage falls were not as marked and the pattern not as consistent as that seen with larger insulin doses. Other workers,[15] using doses up to 10 units showed a consistent fall in eosinophil level comparable in most cases to the response to adrenaline.

PSYCHOLOGICAL FACTORS

The reactions to emotional stimuli and the resulting emotional states are probably the most interesting aspects of this whole field of study for the psychiatrist.

Studying the manic phase of manic depressive psychosis, we have gained the impression that there are two phases of activity to consider, namely, the early stages of the attack before the full-blown clinical picture emerges, and the later stage which may continue for a considerable length of time. In other words, there would seem to be a bi-phasic activity in terms, at least, of the eosinophil level. It is difficult to obtain material in the early stages, of course, since the patient is usually not hospitalized at this time, but in some patients who come to hospital voluntarily, on recognition of early symptoms, and also in some patients who swing from depression to manic excitement while in hospital, studies can sometimes be made.

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Fig. 1 illustrates a manic depressive patient with a history of several previous admissions who came into hospital voluntarily because she felt under pressure and realized that she was again becoming overactive. At this time she showed little clinical evidence of tension but the eosinophil count was definitely in the low range. Shortly after, she became clearly hypomanic and the count rose to middle range figures. During the next month, the eosinophil count rose and continued at a

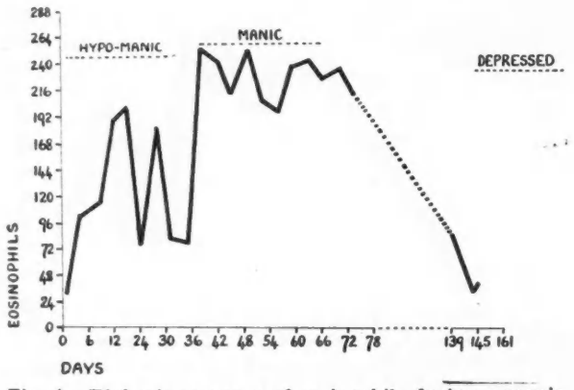

Fig. 1.—Biphasic response of eosinophils during a manic episode.

middle-range level and the patient continued overactive and became more distinctly manic. Then, with few prodromata, she became acutely depressed and this was found to coincide with a remarkable fall in eosinophils to a very low level. Then, following electroconvulsive therapy—not shown in the graph—she regained a normal level of activity, and when discharged her count was in the middle range.

Thus, it would appear from this case and others, that in the manic phase of manic depressive psychosis the period of low eosinophil count might coincide with a period of tension preceding the acute stage, or actually heralding the onset of the attack, whereas the later, higher levels may represent a "resting" or exhaustion phase. Similarly, it is possible that a sudden drop in eosinophil count recorded after following the patient for some time may herald a relapse or the onset of a depression.

It is difficult to make definite statements with respect to common findings in schizophrenia. Tense, and acutely ill patients often show low eosinophil counts but the majority of the cases we have tested here tended to be in the middle or upper range.

In our investigation, we have found that patients with a diagnosis of depression, whether reactive or endogenous, tend to have an eosinophil count in the low range, that is, below 100 and usually below 75. The average count in twenty depressed patients was found to be 55.3, only 1 of them had a count over 100. The eosinophil count in a number of these patients was followed closely over a period of weeks or months and it is interesting to note that clinical improvement is usually accompanied or preceded by a rise in the eosinophil level.

Only one exception to this general rule was seen in our study and occurred in a patient with involutional melancholia who left the hospital clinically recovered but with an eosinophil count that had remained in the low range throughout her stay. This patient was re-admitted to hospital shortly after discharge as she had relapsed into an acute depression almost immediately.

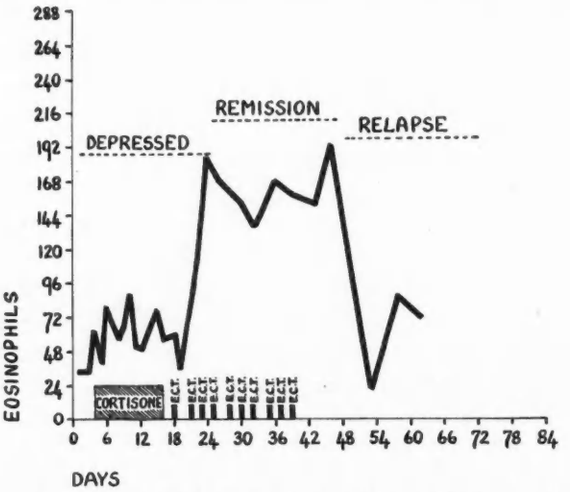

Fig. 2.—Eosinophil response to therapy during a depressed episode. Remission followed by relapse.

Fig. 2 shows a graph of serial eosinophil counts on a 50 year old woman with the typical symptomatology of involutional melancholia. Initial eosinophil counts were all in the low range and despite a relative increase while under treatment with cortisone remained in this range until electroconvulsive therapy was instituted. No clinical improvement was noted while under treatment with cortisone and the slight increase in eosinophils may be ascribed to the "rebound" effect following initial lowerings of the count. With electroconvulsive therapy a remission occurred, coinciding with an elevation of the eosinophil count well into the middle range. Some seven to ten days after the last electroconvulsive treatment of the series, she suddenly relapsed and this was seen to correspond to a sharp drop in eosinophils to the lowest level recorded during her investigation.

Fig. 3 shows variations in eosinophil counts in a 52 year old woman admitted with a diagnosis of manic depressive psychosis, depressed phase. Initial eosinophil counts were low and she was given cortisone experimentally to evaluate any clinical effects on the depression. The eosinophil level at this time fell sharply at first, then gradually climbed to the middle range but no alleviation of the depression was observed. Electroconvulsive therapy was then instituted and she became brighter, more cheerful and regained her appetite. During this period, the eosinophil count went well into the middle range but a sharp fall occurred after four electroconvulsive treatments, corresponding to an acute relapse with exacerbation of former symptoms. A transient paranoid episode, with some diminution of tension coincided with a second transient rise of eosinophils. She remained depressed with eosinophils at the lowest level since hospitalization until a further course of electroconvulsive therapy following which her eosinophil count gradually attained and maintained a middle range value, corresponding to the final recovery from the depression. Shortly after this, she was discharged and has remained well to date.

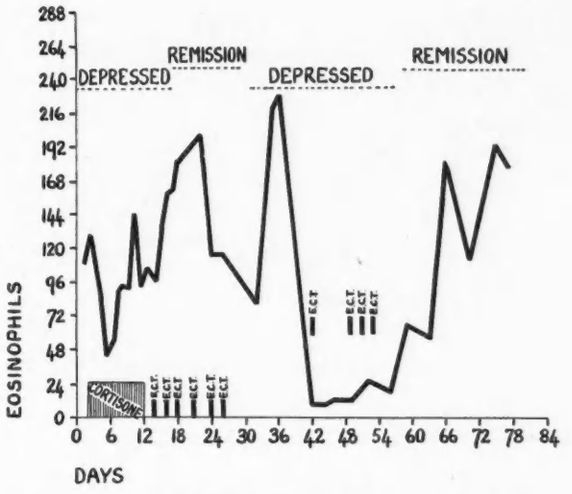

Fig. 3.—Fluctuations of eosinophil at various stages of an intermittent depression.

One of the most clearly outlined features observed in this study consists in the finding that increased emotional tension corresponds with low eosinophil counts. For example, tense paranoid patients tended to be in the low range. All our depressed patients were tense. In our control cases who did not show any obvious emotional pathology, there was the suggestion of an inverse relationship between eosinophil count and the habitual tensional level. Further evidence of this tendency may be seen in individual patients in which this low eosinophil level was found one or two days preceding a relapse or preceding or accompanying an acute crisis in their illness.

Results with psychotherapeutic interviews, inhalation of nitrous oxide, and various sedatives and other drugs have so far been equivocal. Counts done before and after these procedures or drugs have not shown any consistency of result. It can be said, however, that the eosinophil count with each procedure showed a rise in some individuals who subjectively experienced a noticeable amount of relief of tension and a feeling of increased well-being. In patients in whom there was little or no emotional change there was also no significant eosinophil change.

For the psychotherapeutic interviews, in order to establish the general trend of eosinophil counts a count was taken one hour before the interview and again immediately before the interview. The final count was made just after the one-hour interview. This method is to be recommended as a means of control in order not to be misled by the possibility of physiological variations or variations due to the tension or relaxation inherent in the pre-interview situation.

Discussion

In the interest of accuracy and control, emphasis should probably be placed on the concept of longitudinal studies in this field, rather than cross-sectional. Thus it would be more satisfactory to take many counts on a day-to-day basis, to establish a baseline and a "trend", and continue in this manner when investigating effects of specific treatments and procedures.

The emphasis hitherto has been placed on drugs and agents which stimulate the adrenal cortex and which produce evidence in the blood or urine of increased adrenocortical activity. It is our belief that the psychiatrist should also be concerned with techniques and agents which tend to raise the eosinophil count since this might possibly serve as a means of relieving tension and anxiety. This rise in eosinophils and the possible inhibition of adrenocortical activity might come about by psychotherapeutic techniques or by certain specific drugs. Some of our findings suggest that the feeling of relaxation and well-being may be associated with a relatively increased eosinophil count. The most efficacious and best-controlled means of securing this would seem to be a fruitful topic of investigation.

As another future possibility, studies might be carried out on the use of the eosinophil count as a routine psychiatric procedure on new admissions to hospital or in private practice where it may serve as an adjunct to diagnosis and treatment of the patient's tensional level and emotional status. In judging a patient's recovery from a depression, for example, one might do well to consider whether or not a rise in eosinophil level has occurred.

Summary

1. Spontaneous diurnal variations and the intrinsic error of the count have to be considered in evaluating the eosinophil level.

2. Caution is indicated in relating the eosinophil level to adrenocortical function, stress, and emotional conditions.

3. Of all physiological factors investigated, insulin coma therapy was found to result in the most profound eosinopenia.

4. The concept of a low, middle and upper "range" of eosinophil level is suggested, corres-

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ponding to counts from 0 to 100, 100 to 200, 250 and above, respectively.

5. Eosinophil counts in the upper range are less significant from the psychiatric point of view, but sometimes occur with mood shifts towards a feeling of relaxed well-being.

6. Manic attacks in the manic depressive often show a bi-phasic activity in terms of the eosinophil level.

7. Depressive attacks tend to be associated with eosinophil counts in the low range and clinical improvement or relapse closely parallel changes in the eosinophil count.

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REFERENCES

1. ROCHE, M., THORNE, G. W. AND HILLS, A. G.: *New England J. Med.*, **242**: 307, 1950.
2. BEST, W. R. AND SAMPTER, M.: *Blood*, **6**: 61, 1951.
3. HILLS, A. G., FORSHAM, P. H. AND FINCH, C. A.: *Blood*, **3**: 755, 1948.
4. ELMADJIAN, F.: *Am. J. Psychiat.*, **106**: 651, 1948.
5. RUD, F.: *Acta. Psychiat. et Neurol.*, Suppl. **40**: 1947, Quoted by Best and Sampter, *Ibid.*
6. PINCUS, G., ROMANOFF, L. P. AND CARLO, J. A.: *J. Clin. Endocrinol.*, **8**: 221, 1948.
7. FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. AND HILLS, A. G.: *J. Clin. Endocrinol.*, **8**: 15, 1948.
8. RECENT, L., FORSHAM, P. AND THORNE, G. W.: *J. Clin. Endocrinol.*, **8**: 589, 1948.
9. PINCUS, G. *et al.*: *Psychosomatic Med.*, **11**: 74, 1949.
10. FREEMAN, H. AND ELMADJIAN, F.: *Am. J. Psychiat.*, **106**: 660, 1949.
11. STEIN, M., RONZONI, E. AND GILDEA, E. F.: Unpublished data read at the American Psychiatric Association Convention, Cincinnati, O., May, 1951.
12. PINCUS, G. *et al.*: *Am. Research Nerv. & Ment. Dis.*, **29**: 469, 1950.
13. RASKIN, N., HOWARD, G. AND SINGER, S.: *Am. J. Psychiat.*, **107**: 758, 1951.
14. ALTSCHULE, M. D., PARKHURST, B. H. AND TILLOTSON, K. J.: *J. Clin. Endocrinol.*, **9**: 440, 1949.
15. LARAGH, J. H. AND ALMY, T. P.: *Proc. Soc. Exper. Biol. & Med.*, **69**: 499, 1948.
16. CLEGHORN, R. A. AND GRAHAM, B. F.: *Am. J. Psychiat.*, **106**: 668, 1950.
17. RENOLD, A. E., QUIGLEY, T. B., KENNARD, H. E. AND THORNE, G. W.: *New England J. Med.*, **244**: 754, 1951.

PRIMARY AMYLOIDOSIS SIMULATING CIRRHOSIS OF LIVER*

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AMYLOIDOSIS IS A TERM loosely used to describe an amorphous, homogeneous, eosinophilic substance occurring in connective tissue of various organs. Usually it stains metachromatically with methyl violet and methyl green, yellow or faint pink with Van Gieson and it has an affinity for the congo red stain. It is thought to be composed chiefly of protein-like material combined with amino acids and a small proportion of polysaccharide similar to chondroiton sulphuric acid.[2, 5] However, it has been shown by Hass and co-workers[6] that it may vary qualitatively under different conditions. The pathogenesis of amyloid deposition in tissue is not at all clear but is thought to represent an obscure derangement of protein metabolism. This is supported by its occurrence in cases of multiple myeloma with hyperglobulinæmia and in horses which have been used to produce various antiserums in which there is also a marked rise in the serum globulin.

A clinico-pathological classification of amyloidosis has been suggested by Dahlin[2] which would appear satisfactory until more is learned of this condition.

1. Primary amyloidosis: (a) systemic; (b) focal or tumefactive.
2. Amyloidosis complicating myeloma: (a) systemic; (b) focal or tumefactive.
3. Secondary amyloidosis.

Amyloidosis has long been known to occur secondary to long-standing suppurative disease of bone, pulmonary and osseous tuberculosis and numerous other disease processes such as chronic syphilis, malignant tumours, rheumatoid arthritis, chronic ulcerative colitis, subacute bacterial endocarditis, etc. The deposition of amyloid in secondary amyloidosis most frequently occurs in the liver, spleen, kidneys and adrenals.

Primary systemic amyloidosis as classified by Lubarsch[8] is characterized by involvement of the cardiovascular system and tissues of mesodermal origin in the absence of chronic illness. According to Dahlin[3] it differs from the more common secondary amyloidosis in several respects: (1) absence of the generally considered specific etiological disease process; (2) minimal involvement of the liver, spleen, kidneys and adrenals; (3) considerable deposition in the heart, lungs, skin, striated muscle and other tissues infrequently involved in secondary amyloidosis; (4) atypical reactions to amyloid stains and (5) the occasional occurrence of amyloid tumours. However, the line of distinction between primary and secondary amyloidosis is not as clear cut as originally portrayed. Dahlin[3] has reported six cases of primary amyloidosis in each of which there was an absence of a pre-existing etiological disease and the cardiovascular system showed an in-

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volvement with amyloid to a greater or lesser degree. Five of his cases had marked amyloidosis of the liver; five had diffuse splenic infiltration and three had renal and adrenal infiltration. All six patients presented dependent œdema, while four had ascites and one had jaundice.

Because of the obvious overlap between primary and secondary amyloidosis Dahlin[3] concluded that of all the criteria given for the diagnosis of primary systemic amyloidosis the absence of pre-existing or etiologic disease is the only constant clinical and pathologic finding.

Recently we have seen a case which showed a bizarre distribution of amyloid infiltration which is thought to be of the primary type because of the unusual staining characteristics and the lack of any co-existent disease process to which it could be related. The clinical features of this case were entirely those of liver cirrhosis with portal hypertension.

CASE REPORT

This 84-year old Frenchman was first seen in February, 1950, complaining of a slightly tender swelling in the right breast which had first been noticed approximately one month previously. There had been no bleeding or discharge from the nipple and no history of trauma. Physical examination revealed a thin, very alert male weighing 132 lb. with a history of an 8 lb. weight loss during recent months. The pupils were regular, round and equal and reacted to light and accommodation. The head and neck were normal. The right mammary gland was diffusely enlarged measuring 4.5 x 3.0 cm. It was not fixed to the skin or underlying fascia. It was slightly tender on manipulation. The left breast was normal and there was no evidence of axillary lymphadenopathy. The lungs and heart appeared normal. The blood pressure was 140/80, pulse 80 per minute. The liver extended 3.0 cm. below the costal margin; it was firm and non-tender. There were no other palpable masses and at this time ascitic fluid was not demonstrable. Both lower extremities showed varicose veins. The genitalia were normal. Rectal examination revealed a moderately enlarged prostate. A clinical diagnosis of gynæcomastia possibly due to an underlying cirrhosis of the liver was made.

Laboratory findings.—X-ray examination of the chest and gastro-intestinal tract revealed no lesion. The blood Kahn was negative and the hæmoglobin was 14.5 gm. %. The total bilirubin was 0.5 mgm. %. Alkaline phosphatase 13 King Armstrong units; thymol turbidity 4 units; thymol flocculation plus 2 and total protein 6.6 gm. % with albumin 4.0 gm. and globulin 2.6 gm. The urine urobilinogen was 1.5 mgm. %, there was no bile pigment but bile salts were present. Urinalysis revealed a specific gravity of 1:016; pH was 5.5; there was a trace of protein, no acetone or reducing substances. Microscopically, the urine showed plus 1 white blood cells and an occasional hyaline cast.

Progress.—Over the ensuing months he was seen repeatedly by his physician, during which time he developed abdominal distension and ascites became demonstrable. His general condition progressively deteriorated and he was admitted to hospital January 17, 1951.

Physical examination at this time revealed essentially the same findings as those reported above but there was now slight abdominal distension with shifting dullness. The liver had not enlarged further and was still firm and non-tender. The total proteins were now 5.7 gm., albumin 3.3 gm. and globulin 2.4 gm. The white blood count was 7,000 with 78% polymorphonuclears, 13% lymphocytes, 4% monocytes, 2% eosinophiles and 3% basophils. The sedimentation rate (Westergren) was 17 mm. per hour. X-ray of the abdomen revealed a hazy appearance of the soft tissue structures of the abdomen compatible with the diagnosis of ascites. On January 21, the patient developed a fever with clinical evidence of bronchopneumonia and despite chemotherapy he died 24 hours later.

AUTOPSY

Each pleural cavity contained approximately 150 ml. and the peritoneal cavity 1,500 ml. of opalescent fluid. The right lung weighed 1,200 gm. and the left 1,140 gm. Both showed a pneumonic consolidation of the upper lobes with basal congestion. The heart was slightly enlarged, weighing 400 gm. and the left ventricle displayed a moderate degree of concentric hypertrophy. The myocardium appeared normal and was not considered to be unduly firm. The endocardium and valves appeared normal. The liver was diffusely enlarged (2,040 gm.) but maintained its normal contour except that the inferior edge of the right lobe was thickened and rounded. The external surface displayed a fine "morocco leather" nodularity and was yellowish-brown in colour. It was extremely firm and the cut surface was waxy and translucent, with a homogeneous, yellowish-brown colour. The spleen weighed 300 gm., was firm and its cut surface was paler than normal. Both kidneys were enlarged, the right weighing 240 gm. and the left 200 gm. Both were of normal shape and extremely firm. The capsules stripped with ease and without decortication leaving a pale and finely granular surface. On section the cortices measured 1.0 cm. in thickness. They were pale, waxy and translucent and not sharply demarcated from the adjacent medulla. There were no gross lesions of the adrenals, pancreas, prostate or gastro-intestinal tract. Portions of the liver and kidney turned a mahogany brown when placed in Gram's iodine containing 1% acetic acid.

Histology.—With hæmatoxylin and eosin stain the liver presented a very large quantity of a homogeneous, eosinophilic staining material dispersed throughout its parenchyma, distorting the normal lobular network and causing a marked atrophy and disappearance of epithelial cells (Fig. 2). This change was diffuse throughout the liver. An occasional island of regenerated liver cells was demonstrated but the usual microscopic picture was that of a few strands of parenchymal

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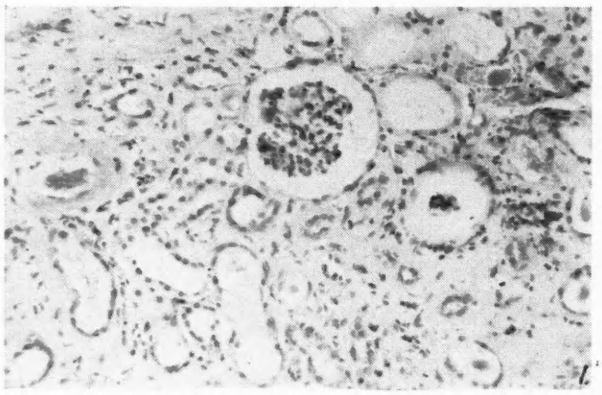

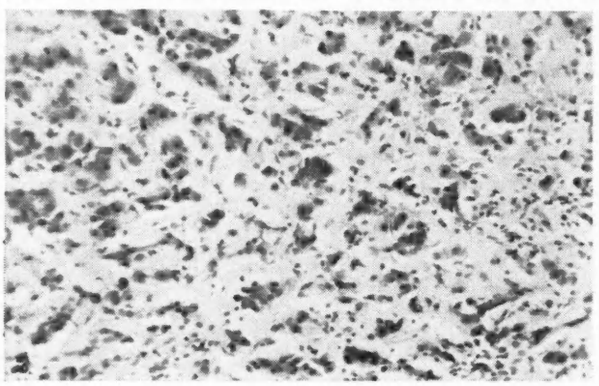

Fig. 1.—Kidney showing tubules widely separated by amorphous material. Note glomerulus uninvolved. Hæmatoxylin and eosin stain. X 120. Fig. 2.—Liver showing epithelial cells widely separated by amorphous material. Hæmatoxylin and eosin stain. X 120.

cells isolated by a dense, structureless matrix. The arterioles showed an eosinophilic smudging. There was no bile duct proliferation. The spleen also showed a diffuse infiltration of the splenic pulp with the same homogeneous, eosinophilic staining substance. The blood sinusoids as a result were widely separated. The Malpighian corpuscles were readily demonstrated and appeared uninvolved. Kidneys: the glomeruli showed some shrinkage of the tufts but not the usual basement membrane thickening associated with amyloidosis. The tubules were small, atrophic and widely separated by greatly increased interstitial tissue of the same homogeneous appearance encountered in the liver and spleen (Fig. 1). The arterioles also showed marked eosinophilic smudging. Adrenals: the parenchymal cells were indistinct and widely separated by a similar eosinophilic material. The small arteries in the adrenal capsule were thickened and smudged. The pancreas revealed a mild increase in homogeneous connective tissue. The myocardium showed minimal involvement with only an occasional thin strand of homogeneous, eosinophilic staining material passing between the myocardial fibres. Sections of lungs, tongue and striated muscle did not show any material suggestive of amyloid.

Special stains were used in an endeavour to identify this homogeneous substance. It stained yellow with Van Gieson, pale grey-blue with Mallory's aniline blue method and a very pale grey-green using Masson's trichrome stain containing light green. It thus reacted differently to collagen. Wilder's reticulin method showed no precipitation of silver. It failed to react with the periodic acid-Schiff reagent described by McManus[9] while control slides of a nephrosclerotic kidney showed hyaline arteriosclerotic vessels to be a deep violet purple, thus showing the substance was different from the usual "hyaline" material.

Congo red stained it a light pink while occasional arterioles were deeper red. Methyl and crystal violet proved most capricious. In some of the many sections stained, methyl violet gave a dull violet tinge to the material in the heart, liver, spleen and kidney. In contrast to this reaction, control material from other cases of secondary amyloidosis and corpora amylacea in the prostate of this man stained a brilliant violet.

It was felt that these reactions probably indicated the material to be an "atypical amyloid". Because of the unusual distribution of the substance in the kidney and the somewhat controversial staining reactions, blocks of tissues were reviewed for us by Dr. D. C. Dahlin of the Mayo Clinic who reported that he considered the reaction with methyl violet and Bannon's toluidine blue to be typical of amyloid. He also noted that he had observed a similar distribution of the amyloid substance in the kidney in an occasional example of his group of primary amyloidosis.[4]

It was therefore concluded that we were dealing with an instance of primary amyloidosis in which both the cardiovascular system and parenchymal organs were diffusely involved, the latter to a greater degree than usual. It was most unfortunate that the bone marrow was not examined. However, a review of x-rays that included ribs, sternum and vertebræ showed no bony lesions and the hæmatologic studies showed nothing to support bone marrow involvement so that we feel that myelomatosis as a cause of the amyloid degeneration can probably be ruled out.

DISCUSSION

In the above case, the striking histopathology was the presence of a diffuse, homogeneous, eosinophilic substance involving the connective tissue of various viscera and suggesting amyloidosis. However, this substance accepted only a few of the so-called typical "amyloid stains". This obvious disparity in the staining qualities of a substance which morphologically resembles amyloid suggests the possibility of qualitative differences between what is termed "primary" and "secondary" amyloidosis, or that, in fact, there is more than one amyloid substance. But what is amyloid? It has been pointed out that all the eosinophilic, homogeneous extracellular substances which stain similarly with congo red, iodine and acid, and methyl violet are classified as amyloid and although on this basis, the term "amyloid" is perhaps justified it does not prove these substances to be of similar composition or pathogenesis.[7] Of these extracellular homogeneous and metachromatic substances, the mucopolysaccharides appear to be of greatest significance and it is possible that "amyloid" is a mucopolysaccharide combined with a variety of different proteins including those of reticulin as well as those involved in the antigen-antibody reactions.[7] Wolbach[10] has observed that collagen and reticulin also develop from metachromatic extracellular material which he terms "amorphous collagen". It is possible that amyloid, reticulin and collagen may be variants of a fundamental biochemical process in the extracellular connective tissue. It has been proposed by Altshuler and Angevine[1] that the fibrinoid degeneration in rheumatic fever and rheumatoid arthritis is a precipitation of acid mucopolysaccharides of the connective tissue ground substance and it is thus possible that there is some basic similarity between amyloidosis and the so-called "collagen diseases". Jones and Frazier[7] have noted that although amyloid and hyaline are similar morphologically, there does not appear to be any pathogenic relationship. They suggest that the term "amyloid" probably includes a variety of substances related to one another only as a manifestation of an alteration in a basic extracellular mucopolysaccharide-reticulin response.

From the foregoing it is felt that sufficient knowledge has accumulated to suggest that there may be a close relationship between "amyloid degeneration" and other disease processes which basically effect the extracellular ground substance. The probability is that such changes represent alteration in the chemical constitution of ground substance or connective tissues as a result of which they appear as amorphous, homogeneous eosinophilic material in routine histological sections stained with eosin.

At the present time the term amyloid degeneration should imply such a chemical alteration, the resulting substance being identified as amyloid by its ability to react with the "amyloid stains". Minor variations in the chemical constitution of the "amyloid substance" could then lead to variations in staining characteristics as seen in this case and in others variously termed atypical amyloidosis, paramyloidosis and hyalinosis.

SUMMARY

1. A case of primary "atypical amyloidosis" is presented in which the clinical features were those of portal cirrhosis.

2. The staining reaction of the homogeneous, eosinophilic, interstitial material which involved the liver, spleen, kidneys, adrenals to a marked degree are discussed and the possibilities of amyloidosis being an alteration in the extracellular mucopolysaccharide-protein complex are reviewed.

REFERENCES

1. ALTSHULER, C. H. AND ANGEVINE, D. M.: *Am. J. Path.*, **25**: 1061, 1949.
2. DAHLIN, D. C.: *M. Clin. North America*, **34**: 1107, 1950.
3. *Idem*: *Am. J. Path.*, **25**: 105, 1949.
4. *Idem*: Personal communication.
5. HASS, G.: *Arch. Path.*, **34**: 92, 1942.
6. HASS, G. M., HUNTINGTON, R. AND KRUMDIEK, N.: *Arch. Path.*, **35**: 226, 1943.
7. JONES, R. S. AND FRAZIER, D. B.: *Arch. Path.*, **50**: 366, 1950.
8. LUBARSCH, O.: *Virchow Arch. Path. Anat.*, **271**: 867, 1929.
9. MCMANUS, J. F. A.: *Am. J. Path.*, **24**: 643, 1948.
10. WOLBACH, S. B.: *Am. J. Path.*, **9**: 689, 1933.

3,000 STUDENTS HELPED BY INTERNATIONAL EDUCATION INSTITUTE.—Scholarships provided by the Institute of International Education in New York, enables more than 3,000 persons from over sixty countries to carry on special studies, according to Kenneth Holland, former American delegate to UNESCO and newly-elected president of the Institute.

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ACTH AND CORTISONE THERAPY IN EYE DISEASE*

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ACTH AND CORTISONE in the treatment of inflammatory eye disease have been favourably reported by numerous authors. Early workers in this field, namely Gordon and McLean,[1] Woods,[2] Steffensen and co-workers,[3] Henderson and Hollenhorst,[4] and many others, found these hormones to be remarkably effective in a wide variety of inflammatory diseases of the external and inner eye. The most favourable response to hormones occurred where the allergic factor was prominent, as reported by Thygeson and Fritz[6] in phlyctenular conjunctivitis and in vernal catarrh.

In the experimental field, Woods and Wood[7] have reported the blocking of inflammatory reaction in rabbits by cortisone, where bacterial and other foreign protein was injected into the eye. Biegel[8] has shown that the daily administration of cortisone intramuscularly has a suppressing effect in most of the features of horse serum uveitis in rabbits.

Thygeson, Geller and Schwartz,[9] working with herpetic keratitis in rabbits, were unable to show any favourable response to cortisone administered intramuscularly, subconjunctivally or by local instillation. Ormsby, Dempster and van Rooyen,[10] have shown that intramuscular injection of cortisone in rabbits with herpetic keratitis prolongs the acute phase of the disease, increases its severity and, at the same time, inhibits the invasion into the cornea of new blood vessels.

This report is based upon the experience in 176 human cases of inflammatory disease of the eye treated over a period of twelve months since April, 1950.

METHOD OF ADMINISTRATION AND DOSAGE EMPLOYED

When the anterior segment of the eye was involved, cortisone ointment, 2½%, applied topically 4 times daily, was more effective than the suspension of the same concentration in saline (1 drop every hour). Subconjunctival injection of 8 mgm. (1/3 c.c. of 2½% cortisone suspension) was occasionally painful, but obviated the frequent applications of ointment or drops and could be repeated every four or five days. The relative merits of these three methods would seem to depend on such factors as concentration of the drug and faithfulness of application, rather than on the actual method used.

Intramuscular cortisone or ACTH, or oral cortisone were effective in most anterior segment inflammations, but the keratic precipitates and the aqueous flare disappeared much more rapidly with topical ointment or drops. When treatment of the posterior segment was indicated, topical cortisone was without effect and intramuscular or oral therapy was necessitated.

The degree of inflammation determined roughly the dosage employed. Mild attacks of iritis responded to topical cortisone in most instances, but in our most severe cases 400 mgm. of cortisone daily, combined with topical drops, was necessary to control the inflammatory process. Recommended dosages are given in Table I.

TABLE I.

AVERAGE DAILY DOSAGES

Inflammatory reaction	*Cortisone (Merck)*		*ACTH (Armour)*
	Intramuscular	*Oral*	*Intramuscular*
Mild	100 mgm.	150 mgm.	100 mgm.
Severe	200-300 mgm.	300-400 mgm.	100-200 mgm.

BACTERIOLOGICAL AND VIRUS EXAMINATIONS

Lid cultures and scrapings were taken in all external diseases. Staphylococcus aureus was frequently encountered and we found it necessary to treat the coagulase positive strains with antibiotics. Failure to improve on topical cortisone was not infrequently due to the superimposed infection and our observations would suggest that, in at least some cases, the tissue defences to these organisms are inhibited by cortisone and ACTH. Similarly, virus studies were undertaken in all suspected herpetic lesions; herpes simplex virus was isolated from six corneal ulcers.

Tonometric readings were taken in the majority of cases and finger tensions in all. No instances of increased tension in the entire series could be attributed to this form of therapy. This finding is of interest in view of case histories

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reported in the literature in which the ocular tension was increased during cortisone therapy (see Hogan *et al.*[11]).

UVEITIS

Fifty cases of iritis and chorio-retinitis were treated. Atropine ointment was used as an adjuvant in acute cases only. Hormone therapy did not appear to shorten these conditions (since exacerbations occurred if it was discontinued too soon), but it did reduce the symptoms and the sequelæ. The only failures were two patients with secondary glaucoma, but even in these the pain and inflammation were relieved by cortisone therapy, although the ocular tension remained unchanged.

Complete remission of the inflammatory process occurred in all but 5 of the 50 patients with uveitis (Table II). Incomplete remissions were accounted for by inadequate dosage in three patients in whom high dosage was contraindicated. Relapses, the result of discontinuing the use of hormones too soon, were quickly brought under control by resuming therapy. Two typical case histories follow:

TABLE II.

EFFECT OF HORMONES ON VARIOUS TYPES OF UVEITIS

Type	*Etiology*	*Anterior*	*Posterior*	*Complete remission*	*Incomplete remission*	*Relapse*	*Failure*
Non-granulomatous	Associated with arthritis	16	2	6	2	2	1
	Unknown	5	4	9	0	0	0
	Gonorrhœa	2	0	2	0	0	0
	Postoperative	10	0	5	0	0	0
Granulomatous	Sarcoidosis	3 (anterior and posterior)		3	0	1	0
	Sympathetic	5 (1 anterior and posterior)		4	1	1	1 (secondary glaucoma)
	Suspected T.B.	3		2	0	1	0
Totals		44	6	31	3	5	2

CASE 1

F.M., male, age 34, was diagnosed Heerfordt's disease December 18, 1950, because of bilateral enlargement of the parotids and benign uveitis with mutton fat keratic precipitates in both eyes. Histopathologic examination of an axillary lymph node was positive for sarcoid. The visual acuity was 6/6 in both eyes at that time, but had dropped to 6/24 in both eyes by September, 1950, and heavy keratic precipitates, vitreous floaters and retinal œdema were present in both eyes. A three weeks' course of cortisone intramuscularly (100 mgm. daily) cleared the retinal œdema and the ciliary injection, but the keratic precipitates remained. ACTH, 10 mgm. q.i.d., was commenced October 14, 1950, and increased to 15 mgm. q.i.d. in one week. This was continued for three weeks, at which time he developed an allergy to hog protein and it had to be discontinued. Histopathologic examination of another lymph node at this time was still positive for sarcoid. There was a severe flare up of the iritis on discontinuing the injections. On December 4 cortisone ointment was started and after 14 days only a few keratic precipitates remained and the visual acuity had improved to 6/7 in both eyes. At the time of writing the generalized sarcoidosis is still active and cortisone ointment is periodically employed with success to control the iritis.

CASE 2

A.R., male, age 33, was under treatment for active Marie-Strümpell arthritis when admitted to hospital with acute iritis in the left eye. A flocculent exudate filled the anterior chamber. He failed to show any response to the usual course of atropine, salicylates and fever therapy over a period of seven days. On June 22, 1950, intramuscular cortisone (300 mgm.) was given and repeated in 24 hours. The pain had disappeared within 8 hours. The dosage was reduced to 200 mgm. daily. The flocculent exudate had disappeared on the third day and the keratic precipitates on the fourth day. A slight aqueous flare persisted for 10 days, during which time the cortisone was reduced to 100 mgm. daily. He was then discharged from hospital completely free of all signs of his uveitis (24 days in hospital).

He was readmitted 1 week later with a dense aqueous flare in both eyes. Cortisone drops 2½% q.i.d. were administered in each eye with improvement in the left, but the right became steadily worse. Intra-oral cortisone (400 mgm. daily) was given for 6 days and marked improvement occurred. The dose was reduced to 300 mgm. daily for another 4 days and then 200 mgm. daily as a maintenance dose. The iritis flared up on this oral dosage and the intramuscular route (150 mgm. daily) was employed. He again had speedy relief. He was maintained on this dosage for 7 days and this was further reduced to 50 mgm. for another 5 days. He was discharged 43 days after the second admission.

The final visual acuity was 6/6 in each eye and after 12 months there have been no further exacerbations.

KERATITIS

The relief of pain and suppression of the inflammatory reaction were readily demonstrable in all cases of keratitis (Table III). Vascularization of the cornea was invariably inhibited by hormone therapy.

Eleven cases of chemical burn, all severe, obtained relief of pain within 2 to 8 hours of commencing topical cortisone. They healed with minimal scarring and without vascularization. One patient with severe bilateral lime burn, in whom perforation of both corneæ occurred, experienced little pain and developed no granulation tissue in either cornea. In this patient cortisone drops were discontinued after 14 days since no evidence of healing could be seen. It is possible that the effect of cortisone in delaying healing contributed to the perforation in both eyes.

had a three months' and the others more than one month's course of treatment. Another patient was referred to us with an extensive dendritic ulcer of five months' duration. During most of this time he had used cortisone "drops". Two weeks after these drops were discontinued the corneal ulceration healed spontaneously.

Corneal vesicles (staining with fluorescein but not ulcerated) associated with anæsthesia of the cornea and irregular deep stromal infiltrates were encountered in ten instances. The infiltrates cleared rapidly and left minimal residual nebulæ when treated with topical cortisone. We did

TABLE III.

THE EFFECT OF HORMONES ON VARIOUS TYPES OF KERATITIS

Type	*Etiology*	*Complete remission of inflammation*	*Relapse*	*Complications*	*Failure*
Marginal ulcers and infiltrates	Conjunctivitis	8	5		0
	Rosacea	1	1		0
Trauma	Postoperative	3	0		0
	Blast injury	2	0		0
	Mascara injury	1			0
	Chromic acid	1			0
	Nitric acid	1			0
	Chlorine	3			0
	Lime	5		2 perforated corneæ	0
Central ulcer	Herpex (dendritic)			4 extensive late scars	20
Interstitial	Post herpetic infiltrates	10			
	Post herpetic disciform	15	1	1 perforated cornea	
	Lues	7			
	Tuberculous	1			
	Sclerosing	5			
	Acrodynia	1			
	Phlyctenular	1			
	Degenerative				5
Totals (cases 90)		65	7	7	25

In chemical burns, however, where loss of tissue is slight initially, we feel that cortisone is the treatment of choice since it relieves much of the discomfort and prevents the vascularization which causes blindness in so many of these injuries.

Syphilitic interstitial keratitis in the acute phase responds to topical cortisone. The pain and photophobia are rapidly relieved and the blood vessels fail to invade the cornea. Scar tissue and blood vessels, once present, remain permanently.

Twenty cases of dendritic ulcer were treated with topical cortisone. Presumably all of these were caused by infection with herpex simplex virus. In six cases we had successful isolation of the virus. None of the twenty cases appeared appreciably benefited by the cortisone. Ten cases healed slowly and the ulceration involved the entire epithelium. Two of this latter group

not observe any adverse effect on the vesicles.

Acute disciform keratitis with secondary iritis was treated with topical cortisone in fifteen patients. Response was uniform and dramatic. In two of these eyes the condition had been acute for three months and enucleation had been considered before cortisone was started. Another patient had a necrotic disciform lesion and the cornea became ectatic, but the inflammatory symptoms subsided following topical cortisone and he was discharged from hospital. He returned six weeks later with a slough of the entire superficial area. Perforation occurred with the loss of aqueous and required a conjunctival flap.

In one of our fifteen cases of disciform keratitis we observed the dendritic ulcer (successfully treated with iodine cautery) develop 48 hours later an underlying disciform lesion. One subconjunctival injection of 2.5 mgm. of corti-

sone reduced the infiltrate to a nebulous scar and the invading blood vessels were arrested and became mere shadows.

CONJUNCTIVITIS

TABLE IV.

THE EFFECTS OF THE HORMONES ON VARIOUS TYPES OF CONJUNCTIVITIS

Type	*Etiology*	*Complete remission of inflammatory process*	*Relapse*	*Failure*
Follicular	Inclusion blennorrhœa			1
	Vernal catarrh	5	2	0
	Allergic—Butyn	1	0	0
	Penicillin	5	0	0
	Atropine	5	0	0
	Unknown	3	2	0
Catarrhal	Staphylococcus			2

The allergic group of conjunctivitides responded well to topical cortisone. When the allergin could not be eliminated, symptoms returned. Staphylococcal infections of the lids and conjunctivæ were not benefited by cortisone therapy.

CASE 3

A 55 year old male, giving a history of a sore left eye for 3 days, had a blepharoconjunctivitis with superficial corneal erosions. He was given cortisone drops hourly when first examined. Cultures subsequently revealed a heavy growth of coagulase positive staphylococcus aureus. For the next 48 hours he had relief of pain but the swelling and œdema increased. On the third day he was again seen in the clinic and the eye lids were extremely œdematous, there was profuse catarrhal secretion and the cornea was extensively eroded. The disease rapidly responded when cortisone was discontinued and antibiotics administered.

CASE 4

A 35 year old female had been given topical cortisone for a deep keratitis of the right eye. After four days of this therapy she developed a blepharoconjunctivitis in this eye and the lids became so œdematous that the eyeball was obscured. Meanwhile the keratitis had subsided dramatically. Antibiotic therapy was then administered, along with the cortisone, and the staphylococcic infection of the lids was rapidly controlled.

MISCELLANEOUS CONDITIONS

A group of miscellaneous conditions consisting of six patients with episcleritis, two with endophthalmitis, three with Eales' disease, two with optic neuritis and one with subconjunctival lymphoma were treated with hormones. In all of these the response was favourable, but the number of patients in each series is not large enough to enable us to draw any conclusions.

DISCUSSION

Various complications occurred in both parenteral and topical use of these hormones. In the former, one death occurred in our series from peritonitis due to the perforation of an unsuspected chronic diverticulitis. Hypersensitivity to the hog protein occurred in one patient who received ACTH for 14 days. Therapy had to be discontinued in one patient because of nervous upset and in two because of a rise in blood pressure.

In topically administered cortisone, one patient suffered perforation of both corneæ three weeks after a severe lime burn. He had received cortisone for the first 14 days and granulation tissue had been completely inhibited. In two patients acute staphylococcal infections of the lid margins were adversely affected. Grittiness was complained of when the regular cortisone suspension was used topically. This was overcome in the special ophthalmic preparations manufactured by Merck & Co. in which the maximum particle size was 50 microns.

In all cases relief of pain was usually experienced in from two to six hours. Suppression of the inflammatory reaction, when adequate dosage was employed, was usually complete within 24 to 48 hours. Aqueous flare and keratic precipitates were a more reliable indication of activity in uveitis than was the colour of the eye and as long as these persisted it was found unwise to discontinue therapy. Inhibition of granulation tissue was seen in inflammatory lesions of the cornea where, regardless of etiology, these hormones could be used to prevent the growth of new vessels into the lesion from the limbs. Great judgment of their use was necessary in destructive lesions of the cornea, for the inhibition of the healing process led to a weak and ectatic scar. Three of the corneæ perforated for this reason.

CONCLUSIONS

1. ACTH and cortisone are effective therapeutic agents in uveitis, keratitis, and allergic conjunctivitis.

2. Bacterial pathogens in corneal ulcers, endophthalmitis, conjunctivitis or blepharitis must be controlled by appropriate antibiotics, etc., since there is considerable evidence that the tissue defences are inhibited by these hormones.

3. Viral pathogens as exemplified by herpes keratitis should be approached with caution,

since there is evidence to suggest that the use of cortisone may prolong the acute inflammatory phase and delay healing.

4. Topical cortisone is the treatment of choice when hormone therapy is indicated in disorders involving the anterior segment of the eye. ACTH or cortisone parenterally, or cortisone orally is indicated where the posterior segment of the eye is involved. A combination of these routes is occasionally employed in the more acute or resistant cases.

We wish to acknowledge the assistance of the National Research Council which supplied us with ACTH and cortisone used orally and parenterally; Merck & Co. who provided us with specially prepared ophthalmic ointments and suspensions; and to Dr. C. E. van Rooyen, M.R.C.P. and staff at the Connaught Laboratories who co-operated with us so fully in the virus isolations.

REFERENCES

1. GORDON, D. M. AND MCLEAN, J. M.: *J. A. M. A.*, **142**: 1871, 1950.
2. WOODS, A. C.: *Am. J. Ophth.*, **33**: 1325, 1950.
3. STEFFENSEN, E. H., OLSON, J. A., MARGOLIS, R. R., SMITH, R. W. AND WHITNEY, E. L.: *Am. J. Ophth.*, **33**: 1033, 1950.
4. HENDERSON, J. W. AND HOLLENHORST, R. W.: *Proc. Staff Meet., Mayo Clin.*, **25**: 490, 1950; *Tr. Am. Acad. Ophth.*, In press.
5. HOGAN, M. J., ENGLEMAN, E., THYGESON, P. AND KRUPP, M.: *Am. J. Ophth.*, In press.
6. THYGESON, P. AND FRITZ, M. H.: *Am. J. Ophth.*, **34**: 357, 1951.
7. WOODS, A. C. AND WOOD, R. M.: *Bull. Johns Hopkins Hosp.*, **87**: 482, 1950.
8. BIEGEL, A. C.: *Arch. Ophth.*, **45**: 258, 1951.
9. THYGESON, P., GELLER, H. O. AND SCHWARTZ, A.: *Am. J. Ophth.*, **34**: 885, 1951.
10. ORMSBY, H. L., DEMPSTER, G. AND VAN ROOYEN, C. E.: *Am. J. Ophth.*, In press.
11. HOGAN, M. J., ENGLEMAN, E. P., THYGESON, P. AND KRUPP, M.: The Assoc. For Research In Ophth., Nineteenth Scientific Meeting, P. 14.

CASE REPORTS

ACUTE GASEOUS CHOLECYSTITIS*

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ACUTE CHOLECYSTITIS with gas present in the lumen of the gallbladder due to an infection with gas forming micro-organisms is a rarely observed condition. The first case, discovered on operation, was reported in 1908 by Lobingier. The first case diagnosed from an x-ray plate was reported in 1931 by Hegner. Twenty-three cases were found reported in the literature, the majority occurring in the sixth and seventh decades. There were 19 males and 4 females. Eight cases were proved diabetics, suggesting the possibility that arterio-sclerosis and the tendency to thrombosis found in diabetes might play a rôle in the etiology of acute gaseous cholecystitis. The etiological agents in the cases examined bacteriologically were *Clostridium Welchii, Escherichia coli* and anaerobic streptococci and staphylococci. These bacteria are found not uncommonly in specimens of gallbladders submitted for pathological examination. Gordon-Taylor and Whitby found them in 19 out of 100 specimens of chronic cholecystitis. It appears that some additional factor, reducing the resistance of the gallbladder to these anaerobes which are ordinarily of low virulence, is present in cases where acute gaseous cholecystitis develops. The presence of stones, obstruction of the cystic or common duct and thrombosis are probably of importance.

The following pathological changes were observed: The gallbladder at operation was distended by a foul-smelling exudate mixed with gas bubbles. Gas was also found in the submucosa causing a complete separation of the mucosa from the muscularis. The mucosa, deprived of blood supply, underwent gangrene. Gallstones were often present. A pericholecystitis with massive adhesions was a usual complication. A complete gangrene of the gallbladder wall with rupture and a pericholecystitic abscess containing gas were found in one case.

The clinical course did not differ from the one usually seen in acute cholecystitis. The onset was acute with pain and rigidity in the right upper abdomen. Often a mass was palpable in this region. Temperature and moderate leucocytosis with neutrophilia were usually found. Jaundice was rarely observed.

The radiological signs are pathognomonic and are easily explained by the above described pathological findings. In the early stage, gas is seen in the lumen of the gallbladder, and a fluid level can be seen on films taken in the upright position. The gallbladder is as a rule enlarged. Later gas appears in the submucosa in the form of an almost continuous layer along the entire wall of the organ. The gas progressively disappears from the lumen of the gallbladder and the layer of gas in the submucosa is also slowly absorbed. The organ decreases in

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size and finally, after several weeks, all gas is absorbed. Gas outside the lumen in the neighbourhood of the gallbladder indicates perforation and the presence of a pericholecystitic abscess.

Operation was attempted in 15 cases with four postoperative deaths. The remaining 8 cases had medical treatment and all recovered. Surgery in the acute stage seems to be contraindicated unless perforation is present. Operation after the acute symptoms have subsided presents less danger, but a cholecystectomy is difficult due to the numerous adhesions which are usually found. The majority of the authors agree that conservative treatment is the treatment of choice.

Fig. 1

Fig. 2

Fig. 3

Fig. 1.—The gallbladder is distended and outlined by a layer of gas located between the mucosa and the muscularis in its wall. Fig. 2.—Decrease in size of the gallbladder and partial resorption of the gas 5 days later. Fig. 3.—Further decrease in size of the gallbladder and almost complete resorption of the gas after another ten days.

CASE REPORT

E.P., a 70 year old male, was admitted to the Ottawa General Hospital with acute pain in the right hypochondrium. Temperature and pulse were normal; urinalysis, blood sugar and N.P.N. were normal. The sedimentation rate was 113 mm./hour. The clinical diagnosis was acute cholecystitis. On a film of the gallbladder region, taken on May 17, the diagnosis of gaseous cholecystitis was made. The gall bladder was well outlined by a thin layer of gas in its wall and was quite distended. There was no evidence of radiopaque stones. A miniature film of the chest showed quite pronounced elevation of the right diaphragm. A repeat examination 5 days later showed some decrease in size of the gallbladder and partial resorption of the gas. There was no change in position of the gallbladder on films taken in the upright and prone position, the gallbladder lying parallel to the lower border of the liver thus indicating the presence of pericholecystitis. On a third examination, 10 days later, the gallbladder had further slightly decreased in size and the gas surrounding it had been largely absorbed except for small remnants around the fundus.

The patient improved under conservative treatment and was discharged on May 28 with the advice to return to hospital for an operation after a few days. He was readmitted on June 8, 1950, complaining of nausea, vomiting and constant pain in the right upper quadrant radiating towards his right shoulder. His temperature and pulse were normal, the blood count showed nothing abnormal, the urine was negative for sugar and bile pigment. Physical examination revealed marked tenderness on palpation in the right hypochondrium.

At operation on June 10 the gall bladder was found completely buried in adhesions. On opening the gallbladder, numerous small yellow stones and thick whitish-yellow pus were found. When the cavity of the gallbladder was swabbed the entire mucosa came out as if it were lying loose in the cavity. There was no mention of gas in the operative record, probably this was completely absorbed since the last radiological examination eight days previously. No attempt was made to remove the gallbladder, a drain was inserted and the abdomen closed. The patient made an uneventful recovery and was discharged on June 23. He has been symptom free ever since.

Microscopic examination of the gallbladder mucosa removed at operation revealed partial autolysis and in places acute inflammatory change. No bacteriological examination of the gallbladder contents was made.

SUMMARY

A short review of 23 cases of gaseous cholecystitis is presented. One case seen by the author is described. The typical radiological findings are described and illustrated. Conservative treatment in the acute stage is recommended.

BIBLIOGRAPHY

1. CULVER, C. J. AND KLINE, J. R.: *Radiology*, **50**: 536, 1948.
2. ELSEY, E. C. AND HUDSON, H. C.: *Am. J. Roentgenol.*, **63**: 228, 1950.
3. FRIEDMAN, J., RICHARDS, J. A. AND RIGLER, L. G.: *Am. J. Roentgenol.*, **62**: 814, 1949.
4. JEMERIN, E. E.: *Surgery*, **25**: 237, 1949.

SPONTANEOUS EVISCERATION THROUGH VAGINA

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EVISCERATION following surgical treatment is uncommon, the incidence quoted by various authors varying from 0.1 to 2.0% of surgical cases. Spontaneous evisceration through the vagina occurs so rarely that I felt that a recent case that came under my care was worthy of report.

The patient, Mrs. M.D., age 73, was a para 6 gravida 4. She had in the past been operated on twice, a cholecystectomy in 1940 and a vaginal hysterectomy in 1946. She had been feeling well with the exception of a lot of "gas on her stomach" and moderate constipation. She had, however, noticed a protrusion from the vagina which had gradually been increasing in size.

On the afternoon of June 4, 1951, the patient was straining at stool in her home when she felt a sudden "pop", as she described it, in the vaginal region, and looking down saw several feet of intestine hanging into the toilet. Fortunately she did not flush the toilet but wrapped a towel around the intestine and walked back to bed. The family physician, Dr. George McKee, was immediately called and found the patient lying in bed in no evident shock and the bowel still wrapped up in the towel between her legs.

Dr. McKee had the patient admitted to the Emergency Ward at the General Hospital and asked me to see her there. Her condition at this time was good—pulse 90, good colour, blood pressure 150/88. The abdomen was slightly distended but was not tender. Lying between her legs, wrapped up in a towel, were about five feet of small bowel which was of normal colour and showed active peristalsis.

No treatment was given in the emergency ward but the patient was sent immediately to the operating room. Preparations were made for both a vaginal and an abdominal operation and the patient was given a spinal anæsthetic. The towel was then removed and the bowel cleaned by washing it with warm saline. With the patient in the Trendelenberg position, the bowel was pushed back into the abdomen with little difficulty and both penicillin and sulfonamides were placed in the peritoneal cavity.

The herniation had occurred through a tear in the vaginal vault just where the peritoneum was reflected off the bladder. There was a large enterocele present with a very poor posterior wall. I therefore decided to remove the vaginal mucosa completely and make a good supporting perineal floor by completely obliterating the vagina. This was done using forty day chromic catgut after closing the peritoneum with a purse string suture.

The patient stood the operation very well and had a remarkably smooth postoperative course. There was a moderate degree of distension for the first week which was treated with a Levine tube. She was out of bed on the fourth postoperative day and was discharged on the tenth day. I have seen her on two occasions since the operation and she is doing very well. The pelvic floor is well supported and the patient volunteered the information that she felt ten years younger since her operation.

Spontaneous evisceration through the vagina is a very rare condition. I was unable to find any similar case described in the gynæcological text books or literature.

MUCOSAL RESPIRATORY SYNDROME

H. SUGARMAN, M.D. and
D. M. BALTZAN, M.D., *Saskatoon, Sask.*

THE MUCOSAL RESPIRATORY SYNDROME is an acute febrile disease with marked general toxicity and prostration. The striking features are involvement of the conjunctivæ, the mucous membranes of the mouth and throat associated with pneumonitis. A number of cases have been reported in the past ten years. Some of these had combined skin lesions but they occurred following sulfonamide therapy.

Many fatal results are reported and detailed studies failed to show any specific cause. Allergic reactions were suspected in some and on this basis antihistamine therapy was employed. Other cases were treated symptomatically along general supportive lines. Penicillin seemed to have no effect on the course of the disease. Virus infection is suspected but this has not been proved.

The following case is typical of this syndrome.

Miss J.H., aged 14, was in good health until April 20, 1951. She then developed what her mother thought was a head cold. Her head was stuffed up and she had a sore throat. She improved with bed rest, aspirins and hot drinks. She did not receive any sulfonamides.

Four days later she felt worse again and became feverish. Her mouth became sore and swollen and her eyes became red and exuded a conjunctival purulent discharge. A dry, hacking cough developed.

The past history was essentially negative and there was no known allergy.

The patient was first examined on April 24. She appeared very ill and toxic. The temperature was 104° F. There was a marked conjunctivitis with purulent discharge. The mucous membranes of the mouth and lips were acutely inflamed with blister formations (Fig. 1). There was no cutaneous rash and there were no glandular enlargements. There was dullness on percussion of the lower left lung and profuse crepitations were heard on auscultation. The rest of the physical examination was negative. A diagnosis of mucosal respiratory syndrome was made and she was admitted to St. Paul's Hospital.

Laboratory investigations showed: urinalysis microscopically normal, but a heavy trace of albumen was present. Hgb. 84% (13.0 gm.), R.B.C. 4,209,000, W.B.C. 13,500, neutrophiles segmented 42%, band cells 43%, lymphocytes 10%, monocytes 5%, erythrocyte sedimentation rate 27 mm. in 45 mins. Blood cultures were negative. Blood Wassermann negative. Smears and cultures from the mouth showed *Strep. viridans* (alpha) predominating and a few hæmolytic (beta) streptococci.

Fig. 1

Smears and cultures from the conjunctivæ showed pus but no bacterial growth. Sputum cultures showed predominating pneumococci. X-ray of the chest confirmed the presence of consolidation in the left base.

Treatment so far in this syndrome is non-specific. One could not resist the temptation to employ the antibiotics and try antihistamines. She received S.R. penicillin 400,000 units daily intramuscularly combined with aureomycin 250 mgm. four times a day orally for eight days, as well as benadryl 50 mgm. four times a day. The local eye treatment consisted of aureomycin drops. A diluted solution of aureomycin was used as a mouth wash and aureomycin ointment was applied to the lips.

The temperature gradually subsided from 104 on admission to normal in five days, and it remained normal. The cough and toxic symptoms subsided within the first few days. The conjunctivitis cleared up within a week. However, the mouth lesion and the pneumonic process, as followed by x-rays, persisted for two weeks. The lip lesions formed scabs which gradually peeled off. The gums became spongy and bled easily. Oral vitamin C 100 mgm., three times a day was added to her multiple therapy.

SUMMARY

This was a typical case of mucosal respiratory syndrome. There was no history of any allergy. The concept of a primary virus infection and secondary streptococci and pneumococcal involvement of the mouth and lung seems tenable. It seemed that the addition of aureomycin in the therapeutic management hastened recovery.

REFERENCES

1. STANYON, J. H. AND WARNER, W. P.: *Canad. M. A. J.*, **53**: 427, 1945.
2. SCHOEMPERLEN, C. B.: *Canad. M. A. J.*, **56**: 73, 1947.
3. MEAKINS, J. F.: *Canad. M. A. J.*, **56**: 663, 1947.

SPECIAL ARTICLE

THE SECOND INTERNATIONAL POLIOMYELITIS CONFERENCE

A Summary

W. C. GIBSON, M.D., *Vancouver*

THE SECOND WORLD MEETING on poliomyelitis was held in Copenhagen September 3 to 7, 1951, approximately three years after the initial congress in New York, in 1948. The Congress was sponsored jointly by the National Foundation for Infantile Paralysis, U.S.A., and the Danish National Association for Infantile Paralysis. The hosts were the University of Copenhagen and the Danish Medical Association. The Congress was opened by Her Majesty the Queen of Denmark, and opening addresses were given by the Rector of the University and by His Excellency, Professor Niels Bohr, the well-known atomic physicist.

An extremely full and well-planned program was provided for the five to six hundred delegates in attendance from all quarters of the globe. Four symposia and three review sessions composed the main structure of the subject matter presented.

It would be impossible in a review such as this to condense even in the most fragmentary form, the contents of the several dozen papers given during the sessions of this week-long conference. However, some of the outstanding trends in the research presented should be noted since it is doubtful if in any other field there has been such progress made in the last three years. The importance of this three year period lies in the fact that following the 1948 Conference in New York, scientists in many countries addressed themselves to solving the outstanding and central problems in poliomyelitis, rather than the more peripheral questions. It is not to be wondered at, therefore, that the first papers on viruses and their interactions with the host cell should deal with the ultimate matters basic to viruses.

Dr. C. H. Andrewes of the National Institute for Medical Research, London, dealt with the characteristics of viruses which lead us to look upon them as organisms. In some ways a very different view of viruses was presented by Professor Wendell Stanley of the University of California. He discussed the properties of the tobacco mosaic virus, and showed, at a magnification of twelve million times (on the screen), photographs in which it was possible to see in the cross-sections of the rods of tobacco mosaic disease, fractured by supersonic waves, the hexagon-like formation. The concept of this virus, at least, as a giant molecule, was very well presented.

The behaviour of viruses in plants was most ably reviewed by Dr. F. C. Bawden, F.R.S., of

the Rothamsted Experimental Station in England. He dealt, among other things, with receptor substances in the host material, the effect of temperature on virus lesions in the plant, and the differential distribution of various virus diseases in the one plant.

Virus multiplication and variation were discussed by Professor Max Delbruck of Pasadena, California. He gave an interesting description of experiments in which radioactive carbon or sulphur had been used in a study of the successive generations of viruses.

External factors influencing viruses were discussed by Dr. Frank L. Horsfall, Jr., of the Rockefeller Institute. In the discussion which followed his paper, mention was made of certain promising agents now being tried in the limitation of viral multiplication within cells.

A most interesting paper was given by Dr. John F. Enders of Harvard University, concerning tissue culture methods now available for poliomyelitis research. It would appear from his ability to grow poliomyelitis virus on non-nervous tissue *in vitro*, that we must revise, to some extent our views that poliomyelitis is a neurotropic virus.

The disordered responses of motoneurons in the spinal cord were discussed by Dr. D. P. C. Lloyd, also of the Rockefeller Institute in New York.

The nature and severity of lesions in poliomyelitis and the characteristics of both virus and host in determining these factors were reviewed by Dr. David Bodian of Johns Hopkins University.

Dr. Ruth E. M. Bowden from the University of London discussed the anatomical and physiological evidence concerning the time relationship for recovery from paralysis in poliomyelitis. The demonstration by many workers, in biopsies, of the presence of hypertrophied muscle fibres in the remaining muscles following paralysis was contrasted with the lack of any hypertrophy of muscle fibres in monkeys injected with polio infection, probably because the monkeys had received no type of physical therapy of the nature of that administered to humans. The compensatory branching of residual motor nerve fibres in order to innervate muscles which had lost their own nerve was also discussed. The regenerated, as well as the branching fibres of nerves, were of course unmyelinated.

Dr. Phillippe Bouwens of St. Thomas's Hospital, London, gave a detailed comparison between the recovery of muscle following peripheral nerve injury, as against the electromyogram in muscles following poliomyelitis of the anterior horn cells in the cord. It would seem that fibres of small diameter are more resistant to the damage of poliomyelitis than are the large, rapidly conducting fibres.

The symposium on the Coxsackie group of viruses was opened by Dr. Gilbert Daldorf of the New York State Department of Health, which group has had a very close relation to the early observations at Coxsackie, N.Y. In many ways, Coxsackie disease, also known as Bornholm disease (after the Danish island), or epidemic myalgia, resembles poliomyelitis in its early stages, *i.e.*, there are muscle cramps, increase in temperature, and weakness. However, this relatively benign disease is over in about five days, with no sequelæ. The Coxsackie virus resembles that of polio as to size, excretion in the stools, etc. In mice, it has been demonstrated that Coxsackie virus will reduce the severity of poliomyelitis. In New York State, interestingly enough, there have been concurrent epidemics of Coxsackie disease and poliomyelitis for the past four summers.

The differential diagnosis of poliomyelitis was discussed by Professor Robert Debré of Paris, and was followed by Dr. Joseph E. Smadel, of the Army Medical Service Graduate School, Washington, D.C., who dealt with the laboratory aspect of the diagnosis and stated that such procedures as the isolation of the virus and the identification of specific antibodies are still beyond the ordinary bacteriological laboratory,

Dr. Jordi Casals of the Rockefeller Institute then described his long and successful search for an antigen around which to develop a specific complement fixation test for poliomyelitis. The immunological classification of poliomyelitis was described by Dr. Jonas E. Salk, of Pittsburgh, reporting for survey teams in the University of Pittsburgh, University of Southern California, University of Kansas, and the University of Utah. Dr. Salk, in common with many of the speakers at the congress, harked back to the pioneer work of Burnet and his co-workers in Melbourne. It may well be that points of variance between researchers or between clinicians, reporting on separate epidemics, actually stem from the differences between the types and strains of the poliomyelitis viruses involved.

Under the heading of treatment, many controversial things were discussed, such as tracheotomy, prophylactic use of respirators to ward off the fatigue of the intercostal muscles, and carbon dioxide "poisoning" from hypoventilation. Professor H. J. Seddon from the Institute of Orthopædics, London, described his work on the reconstruction of the upper limb in polio patients, and stressed the importance of attacking the bread-winning problem presented by an incapacitated hand, and its priority over other parts of the limb. Provided that good physiotherapy had been employed during the first six months of the recovery phase, there was nothing to be gained by delaying surgical transplantations beyond that date. He mentioned that the electromyograph had borne out this clinical evaluation.

The need for early rehabilitation of the patient through surgical reconstruction of the affected hand was echoed by Dr. Charles Irwin on the basis of his extensive work at Warm Springs,

Georgia. Similarly, attention was called to the value of half-yearly assessment of the posture of young people once affected by polio, in whatever part of the body. Dr. John R. Cobb of New York discussed the remedial treatment of scoliosis in the light of three thousand cases observed in his clinic in New York.

A very useful classification of the phases of poliomyelitis, as a clinical problem, was presented by Dr. Robert L. Bennett of Warm Springs, Georgia, in the course of his paper on physical medicine in poliomyelitis. He suggested that we should speak of: (1) The phase of medical emergency. (2) The phase of neuromuscular recovery. (3) The phase of adaptation to residual physical handicaps. Again the accent was placed on rehabilitation before chronic invalidism can set in.

Miss Alice Bruun of the Danish Ministry of Social Affairs gave an excellent summary of the preparations for rehabilitation which are set in motion in Denmark almost as soon as paralysis is detected in a case. The positive, active elements in rehabilitation were again stressed, and the whole philosophy of "spending to save" was endorsed by the Danish authorities. The psychological aspects of polio were covered in the same session, by Dr. Morton Seidenfeld of the National Foundation in New York.

The problems of immunity and resistance to virus infections were taken up in the fourth symposium, by Dr. Howard Howe of Johns Hopkins University and by Dr. Joseph L. Melnick of Yale University. Professor Ritchie Russell of Oxford then gave one of the most interesting papers of the congress, entitled "Factors Which Influence the Clinical Course of Poliomyelitis". Fatigue of the muscle during the acute phase of the disease was shown to set the stage for paralysis of that muscle. With this in mind, some clinicians would advocate the early use of the respirator. The application of short wave therapy to the spine in polio was blamed for one quadriplegia of very serious proportions. Electric shock therapy in a mental patient was similarly held responsible for a widespread paralysis.

Bearing on the interesting Australian observations of McClosky on paralysis of the recently vaccinated limb during a polio epidemic, Professor Bradford Hill gave an analysis of the Australian and United Kingdom reports on this subject, and outlined the questions which would have to be answered on a large scale in order that the least dangerous method might be applied in the routine pertussis and diphtheria inoculations. Meantime, it seems wise to carry out inoculations against the common routine communicable diseases outside of the polio season.

Under "The Ecology of Poliomyelitis", Dr. J. H. S. Gear of the new Virus Research Institute, Johannesburg, read a very stimulating paper, tracing the distribution of the virus at the various stages of sewage disposal. His work confirmed that of other observers by showing that there are many more people affected by polio in a community than would appear clinically.

Dr. Thomas Francis of the University of Michigan, spoke of the centres and epicentres of virus infection in the community. Dr. Gunnar Olin of Stockholm dwelt on the changing nature of the disease in Sweden. The morbidity rate for the first three years of life was falling whereas cases in the group over 25 years of age have trebled since 1905.

In summary, Dr. John Paul, the well-known virologist of Yale University, painted a hopeful picture on the future of polio research, and instanced the progress made since the first international conference in New York three years ago. The change in our approach to the disease, since the early descriptions by Heine and others, was striking. Instead of thinking of polio as a disease of temperate climates, we must now realize that it is a widespread endemic disease in semi-tropical areas. Most children in Cairo have acquired an important degree of immunity at the age of two years, while the isolated Eskimo may show no resistance at age twenty. The typing of the poliomyelitis viruses, the successful tissue-culturing of them on non-nervous material, and the complement fixation test of Dr. Casals, were all hailed as important contributions to the subject of poliomyelitis.

FOOD AND DRUG INSPECTORS CHECK IMPORTED PRODUCTS.—Inspectors of the federal health department in September and October turned back 63 shipments of adulterated or misbranded food products being imported into Canada. During the same months, 188 shipments of drugs, including 22 lots of cosmetics, were stopped at the border. Twenty-one parcels of drugs containing narcotics were referred to the department's narcotic control division to ensure that they did not contravene the Opium and Narcotic Drugs Act.

Typical of the problems encountered by the inspectors is that an American company manufacturing a gum advertised as a weight-reducer. Such claims are not allowed by the Canadian law. The manufacturer changed the name of his product as shown on the package but continued to advertise the original trade name and to fill orders from stock packaged under the second name. Importation into Canada of these products has been banned.

A number of prosecutions for violations of the Food and Drugs Act and regulation in Canada came to court in September and October. These included adulteration of minced beef by the addition of horse meat, excessive amounts of cereal in sausage, inclusion of saccharin in soft drinks, and over-the-counter sale of drugs requiring prescriptions.—(From the Dept. of Health and National Welfare.)

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(Information regarding contributions and advertising will be found on the second page following the reading material.)

EDITORIAL

THE VITAMINS

It looks now as if we have exhausted the alphabet in the labelling of vitamins. If we are to expect discoveries of yet more of these substances, and there is every reason to believe that we may, their nomenclature will probably be along descriptive chemical or biochemical lines, as in some instances now. The very word "vitamin" has lost much of its original clearcut intention. Perhaps Gowland Hopkins' first title "accessory factor" was the more inclusive after all. But Funk's insistence on their importance to life, as well as his belief that they were amines, led him to coin the term vitamine, which in time was shorn of its final "e" when it became apparent that these were not necessarily amines. Other names were suggested: auximone; nutramine; advitant; ergin; catalin; nutrilite; and so on. But none of these had that mysterious quality which ensures the immortality of successful words. "Nutrilite" has persisted in the literature because it has a special functional meaning not conveyed by "vitamine", but it is hardly met with outside of specialized journals. Even "vitamin" was not expected to remain attached to each substance, for it was thought that as these became identified each would be suitably named. This was Drummond's idea, as far back as 1920. But in avoiding the unwieldy nomenclature of McCollum ("fat-soluble A", "water-soluble B") and suggesting vitamin A, B, C, etc., he started a system which has now become unmanageable. It accounted also for the arbitrary lettering of vitamins. Not until we reached K was there any attempt to link the designation of the vitamin with its properties, and this only fortuitously: K refers to the German *Koagulation*. Others in this class are H, which refers to the denudation of the skin during deficiency (German *Haut* = skin); L for lactation factor; M, a vitamin for monkeys, and P which prevents excessive cell permeability.

The attempt to squeeze the rapidly accumulating vitamins into the alphabet brought about the use of subscript numbers. This was all very well with A, in which the new members were related chemically and physiologically, but in B a large family arose, with as much difference and confusion as one finds in any large family: some are known only by their chemical names; niacin (nicotinic acid: P-P factor); pantothenic acid, biotin, the pteroylglutamates (folic acid, etc.) and so on.

These are only a very few of the confusing mass of terms now attaching to the nomenclature in this field. It is obvious that the older system of lettering is quite inadequate for the growing number of discoveries. These pyramid on each other as the availability of new growth factors in pure form makes possible further experiments, which in turn uncover yet more of these substances.

THE WORLD MEDICAL ASSOCIATION

At the fifth annual meeting of the World Medical Association in Stockholm, Sweden, the President, Dr. Dag Knutson's inaugural address contained a most excellent summary of the place and function of WMA. Dr. Knutson said in part:

"There is today a steady and increasing interchange of ideas between nations and international bodies, such as WHO, ILO, IASS and UNESCO. These organizations becoming more firmly established and by the nature of things, institutions with their own life, exercise a great influence upon national developments, through their own governing boards, which have been given wide terms of reference. Those again, through their emissaries, bring to the international governmental bodies their governmental views, ultimately directing the work. Governments, having overloaded themselves with tasks and being pressed for time as the international bodies want to get on with their work, often do not consult relevant groups within their own countries, and much happens in the field of health-care and that part of Social Security which might be called medical-security as a result of governmental international work, about which the citizen knows little or nothing, be he a doctor or not.

"In a truly democratic world this should not be so, and the task as well as the organization of the WMA have been formed to counteract undesirable repercussions thereof on the life and work of man as well as medical men. The WMA was created to meet the need for letting the doctors' voices be heard in the international choir and your Council has tried to take care of this particular job—to what extent and with what result you have no doubt found out by a careful study of your

documents. If the WMA is to attain its high aims—to help all men to a better state of health, chiefly through contributing to a suitable and appropriate building-up of health care and medical security—its work in the international field is indispensable. But from what has just been said it follows that its activities on the national level, *i.e.*, through its member-associations, is of equal importance, not to say of even greater."

Canada's participation in the work of the World Medical Association is too well known for further elaboration. We propose however, to comment from time to time on the discussions which took place at this fifth annual meeting: they will be published in full in the *WMA Bulletin* edited by Dr. Morris Fishbein.

Editorial Comments

LEAD POISONING IN CHILDHOOD

Lead poisoning is rare in infancy and childhood in Great Britain; the literature reports 12 cases in the past 60 years, while it is common elsewhere, particularly in Australia, North America, and Japan. In the past two years there have been 23 cases admitted to the Hospital for Sick Children, Toronto. The most frequent cause is pica, or the perverted appetite of children who will eat and gnaw anything. Repainted furniture causes much lead poisoning as young children nibble the wood through the layers of paint, which contains 7 to 27% of lead. Cases are reported of plumbism due to the use of lead nipple shields and the use of lead dusting powders. Modern paints do not contain as much lead as formerly, but there remains the danger from old paint on children's furniture and the woodwork of old houses.

Lead encephalopathy is the pathognomonic sign of chronic plumbism, while eye signs are common; the gingival blue line and muscle palsies are rare in children. Blood examination reveals a moderate anæmia, reticulocytosis, punctate basophilia, and excessive normoblasts. Excessive hæmolysis may cause elevation of serum bilirubin levels, while the urine shows protein in traces with glycosuria and acetonuria. These findings may be verified by lead determinations of the blood (normal 0.01 to 0.03 μgm./100 ml.) and urine (normal not over 0.2 mgm./24 hr.). Radiography may show specks of lead pigment in the gastro-intestinal tract and radio-opaque bands of lead deposition in the growing regions of the bones; this is not seen in adults as lead is only deposited in growing bones. The diagnosis may be in doubt, as abdominal pain, constipation, and vomiting are the triad of symptoms which also indicate a surgical emergency. Diabetes mellitus may be ruled out by normal blood sugar levels, intracranial disease, indicated by "cracked pot" resonance of the skull and spreading of the suture lines is also ruled out by the "lead lines" of the growing bones.

The treatment depends on the close relationship of calcium metabolism and lead. Calcium, as milk, should be given in large quantities, three pints of milk per day and calcium lactate by mouth. In encephalopathic crises, manifested by convulsions, coma, and severe colic, calcium gluconate (10 ml. of 10% solution) should be given intravenously. De-leading of children usually precipitates encephalopathy and should not be attempted. The cerebral œdema is reduced by intramuscular magnesium sulphate and intravenous hypertonic glucose along with repeated lumbar decompression. Dimercaprol (BAL) has had questionable success in plumbism. The prognosis is grave as permanent focal or generalized cerebral damage may result, giving rise to blindness, mental retardation, and speech defects. J.A.S.D.

MEN AND BOOKS

JEFFERSON MEDICAL COLLEGE IN 1850

MALCOLM H. V. CAMERON, M.B., F.R.C.S.[C.], *Toronto*

IN A FORMER COMMUNICATION[1] I referred to a box of letters preserved by William T. Aikins one time professor of surgery in The Toronto School of Medicine and, from 1887 to 1895, Dean of the Faculty of Medicine and Professor of Surgery in the University of Toronto. Aikins had graduated from the Toronto School of Medicine in 1848 and obtained his M.D. degree from Jefferson in 1849. His former roommate, student and friend John Howitt of Guelph had graduated from the Toronto School in 1850 and attended Jefferson in the session 1850-1851. Excerpts from the letters he wrote to Aikins give his impressions of Jefferson as he found it at the opening of the term in September, 1850. Other letters, written by former students of the Toronto School of Medicine who were in Jefferson College between 1850 and 1856, contain additional information and, together with those written by Howitt, give a fairly complete account of Jefferson as it was a century ago.

The association of the Toronto School of Medicine and Jefferson College of Medicine is

indicated, to some extent, by a letter from Dunglison to Aikins, which is quoted in full.

Philadelphia June 21, 1852.

Dear Sir—I was glad to hear, by Mr. Lavell, of your movements, in which I have always felt an interest, since I had an opportunity of witnessing your zeal and attainments, and your excellent deportment, whilst you were with us in the Jefferson Medical College; and you, I trust, have a field in which you will be enabled to exhibit these desirable qualities to others.

I have had pleasure in aiding Mr. Lavell in adopting such a plan as may advance his best interests, and still shall be happy to afford him any aid I can.

I have no exact statistical account of our cases; but the enclosed advertisement, which I have prepared, will sufficiently indicate the variety we must have. Of all the surgical cases, operated on, but one died during the last year. It was a case of abscess in the shoulder joint following the operation for hygroma on the foot; but whether the abscess was metastatic, or independent, was not clear. In the year before, in nearly the same number of operations, two only died;—the one a case of hydrocephalus in which puncture was performed, a case of course invariably fatal; and the other, following the operation called "Barton's" for ankylosis of the knee joint, occurring in a scrofulous and miserable subject.

It appears to me sufficiently astonishing that the mortality should be so small after so many operations and many of them of the most serious character.

I need scarcely say that we shall have much pleasure in receiving our Canadian friends, who may be induced to come to us; and the favourable specimens we have thus far had lead us to hope that we may be equally fortunate in the future.

I am, dear Sir,
Yours truly,

Dr. W. T. Aikins,
53 Queen St.
Toronto.

Robley Dunglison

The punctuation of this letter is carefully reproduced. The advertisement mentioned was not found.

Under the date of September 11, 1850 John Howitt writes a long letter to Aikins telling of his journey from Toronto to Philadelphia and of findng shelter in the home of the Reverend Mr. Reller. This room had been occupied by Aikins the year before and a peach tree is within reach of the window.

"I like Philadelphia. I need say nothing about it for you are better acquainted with it than I am. I have seen Drs. Dunglison and Mitchell. They are very kind to me. All the information that I required they gave me. They both speak in the very highest terms of your talents etc. etc. Mitchell sends his most affectionate regards and says that you are never again to call yourself an 'unworthy pupil'. If I were to tell you all they say respecting you I fear that *even* your vanity would be touched. Today I heard a clinique from Dr. Meigs and also one from Mutter. There were several operations performed all of a minor character. I have taken out a ticket for the Philadelphia Hospital. Today I attended for the first time. I was particularly struck with the cleanliness of its wards. The medical gentlemen in attendance seemed to do their utmost to impart information to the students. How very different from those in Toronto*. . . ."

*In Toronto, students from the Toronto School were not noticed by the teachers in Trinity or by those in the University of Toronto. By 1854 the Faculty of Medicine had ceased to function in the University of Toronto and in 1856 the Faculty in Trinity resigned.

In a letter dated September 19, 1850 Howitt speaks of the Pennsylvania Hospital. He started to write Philadelphia but crossed it out so his ticket would be for the Pennsylvania Hospital and the mention of "Philadelphia Hospital" in his first letter is evidently a mistake. In this letter he asks urgently for a certificate from Rolph as to the courses he attended in Toronto.

"We have cliniques at Jefferson twice a week. Old Meigs is a very pleasing lecturer. There is a good deal of poetry about the old boy. He has some strange ideas of his own. Dr. Mutter is a scientific man and a magnificent operator. He handles a knife like a man who is master of his business. As far as I am able to judge the professors of this institution are well worthy of the situations they hold. Pennsylvania Hospital is well conducted. It bears a strong and marked contrast with that of Toronto. Its cleanliness at once attracts your attention. The floors, the beds etc. have an air of comfort. The patients too are treated as they should be. They have all the attention that the sick require. The attendants are all punctual to the moment. I was pleased with the aparatus (sic) they have for the purpose of allowing the convalescent the benefit of fresh air. They have arm chairs set on wheels which are drawn about the walks in the garden at the back part of the building. There they are wheeled about on level walks under the shade of trees in an atmosphere impregnated with the delicious odours of flowers. It will be long ere, in Canada, a poor invalid at a public hospital will get such treatment. Dysentry is prevailing to some extent. Opium and ipecac is their treatment. They ram down that potent narcotic with a vengeance. Often give as much as twelve grains in twenty-four hours and, sometimes, as much as fifteen. I saw one patient yesterday whom I thought they had given a little too much. He was perfectly narcotized. Occasionally a little of the submuriate is combined. I like the method they treat fractures here it is so simple. The fracture box and the long splint answers every case of the lower extremity". . . .

The letter continues with a very adverse criticism of the presentation of Shakespearian plays as shown in a theatre. The thundrous applause that greeted bad rendition of some of his favourite passages disgusted him.

On October 28, 1850 Howitt wrote a long letter and economized by writing across three of the four pages. This makes it difficult to read as the cross writing is heavier than the text it covers.

"Our lectures have now regularly commenced. There is doubtless a deal of talent and useful knowledge among the Professors of Jefferson but there is not one among them equal to Rolph as a lecturer. I am sure that if he were in Philadelphia he would soon get any chair in any of the institutions. There is one thing among the professors that I do not particularly like. That is their extreme vanity. All of them possess it to a considerable degree with one exception. Bache seems indifferent to applause or flattery. But Dunglison and Pancoast love it better than they ever loved their mother's milk. I like Bache as a lecturer better than any one of them. He possesses, in my humble opinion, by far the most Philosophic mind. He is a close and logical reasoner. Had he the power of expression or the flow of language peculiar to Dunglison he would be regarded as his superior. As you remarked he is the personification of (illegible). He is a dealer of facts. First he establishes his premises, or, rather, lays his foundation unwilling to admit a stone that has the least appearance of un-

soundness. With good material he begins his work forming a basis that controversy cannot subvert and upon this slowly he cements the superstructure. This system of teaching chemistry is the best I ever saw. Mutter is a practical man. Meigs has too much poetry in his composition to confine himself to the real. He is brim full of theory and speculation. However he is an acute observer and consequently his long experience has been the source of much useful information.

Jefferson clinic is excellent—have many operations—seen two persons castrated. Many malignant tumours removed—some operations on the eye—Bartram's great operation for ankylosis of the knee and the Bilateral (sic) operation for stone besides many other smaller ones of perhaps more importance to the country practitioner. Mitchell is very kind to me."

Letter dated "Sunday Evening" and evidently written at leisure as the writing is a clear script and easy to read.

"You ask to know if I like Dr. Mutter. I answer that he cannot be beaten. His lectures are the most practical I ever heard. Dr. Mitchell is not very sympathetic. He dodges about too much. I have heard nearly every lecturer in Philadelphia. In my humble opinion there is not one among them who will compare with Rolph. He has a faculty of imparting knowledge which few possess . . . Dr. Pancoast achieved quite a triumph last week. A fellow came in from the country with a dislocated shoulder. It had dislocated under the clavicle. It was of six weeks standing. He consulted nearly all the surgeons in Philadelphia. They all were afraid to meddle with it. At length Dr. Pancoast undertook the reduction. After two hours he accomplished it. The students made old Jefferson ring with their cheers."

There were nearly five hundred students in Jefferson at this time so the cheering must have been impressive. There is no mention of an anæsthetic, which may indicate ether was in general use and anæsthesia taken for granted or that the patient was of extraordinary fortitude.

In 1856 another student reports some interesting statistics: "There are in different medical schools here upward of fifteen hundred students. Jefferson stands at the head in numbers. Jefferson 510, Univ. of Penn. 412, Pennsylvania and Philadelphia Colleges 150 each, Homœopathic 112, Penn University 50; Eclectic 50, Female 30, Philadelphia College of Pharmacy 100. Total 1564."

It would seem that, regardless of the professorial chairs they occupied, the members of staff were general practitioners in the hospital. At least, most of them did surgical operations. Moses Henry Aikins writing in February, 1856 tells of Pancoast's having

"Ligatured the external iliac artery near its bifurcation in consequence of an aneurism of the Femoral Artery a pouch of which extended up beneath Poupart's Ligament beside the iliac. The operation has been seldom performed, I believe, and the patient is doing well."

"Prof. Gross, a few days since performed a very nice operation for a deficient nose. The operation was the Indian one. The patient was brought before the class a week after with quite a respectable nose."

"Professor Gross I will have in a day or two. . . . He is an excellent lecturer. Some of the old students say that he is not quite as eloquent as Mutter, others that he is and that he is equally as good an operator if not better. He has operated four times since I came—two for strabismus, one removing a large tumor from the antrum maxilare and one for calculus."

In other letters this correspondent tells of deaths among the students of his class. One from typhoid and two from erysipelas, one following measles and a gunshot wound in the other: "One of the students being drunk and accidentally discharging a pistol at his roommate." It was as customary to carry bowie knives and revolvers as it was to carry tooth picks.

"We have seven lectures daily except Wednesdays and Saturdays. Those days two hours at the hospital, two college clinics and two lectures in the afternoon."

With this strenuous program about three hundred students from the various schools in Philadelphia attended the Clinic at the Blockley. One of the 1857 letters described the organization of this ancient institution and the efforts being made to have the clinic continued despite a proposal by the Guardians that it should be abolished. Obstetrics at this time was evidently taught only in lectures as "the Lying in department (of the Pennsylvania Hospital) has been given up in consequence of the impossibility of so purifying it after puerperal fever as to prevent its recurrence and that an additional physician and surgeon have been appointed in place of the two accoucheurs."

The same letter tells of a fire in Louisville University department of medicine in which two thousand books belonging to Professor Gross had been destroyed. Many of these were old treatises which could not be replaced.

An attempt has been made to piece out a picture of a famous school of medicine as it operated a century ago.

REFERENCE

1. *Canad. M. A. J.*, **64**: February, 1951.

THERAPEUTIC INDICATIONS FOR VITAMINS IN MIXTURES.—Nutritive failure indicates a failure of an adequate supply of specific nutrients, to all tissues. Vitamins are essential in the process of repair. Motherhood and hard labour increases the needs of vitamins and may lead to shortages. Although vitamins are necessary for life, they by no means take the place of a well-balanced diet in restoring the tissues in a malnourished person. Folic acid, vitamin B_{12} and its family, and the citrovorum (growth-maintaining) factor, should be considered as nutritive factors as well as antianæmic substances. There are 4 principles of therapy in the rehabilitation of nutritional failure: (1) Conditions causing excessive needs for nutrients are removed or relieved whenever possible; (2) Symptomatic treatment and treatment for co-existing disease; (3) A daily diet of 3,000 to 4,000 calories, 120 to 150 gm. protein, and liberal amounts of minerals and vitamins; and (4) Deficiencies are corrected by therapeutic substances, *e.g.*, dried brewers' yeast powder, liver extract, and synthetic vitamins.—Spies, T. D. *et al.*, *Postgrad. Med.*, **10**: 269, 1951.

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THE GENERAL PRACTITIONER SPEAKS*

[*An extract from a private letter to the Editor.*]

". . . FIRST, what you say about general practitioners and their 'resentment' against specialist groups*—I don't think we have any resentment against them; it's a more positive feeling than that. It is that, while we are quite willing that they should have *their* hospital privileges, we want to have *ours* as well. It goes back a lot further than that. The patient is the person to be considered, not the specialist or the G.P. What I mean by that is this: nobody can practise medicine today properly without access to a hospital. How can you treat a diabetic, or a coronary, or any real medical condition, without using a hospital, at first at any rate? (I say nothing of the surgery which a competent G.P. can do just as well as a specialist can, and which he must be allowed to do, within his capacities.) That is the first point: that neither G.P. nor specialist can practise properly, unless he is allowed what you refer to as 'hospital privileges'. I would prefer to say 'the use of a hospital', as one of his major tools, as you put it.

"The next point is one that we often seem to overlook: that is the fact that from 85 to 90% of sick people go first to a G.P. It is of vital importance that the said G.P. be as competent a diagnostician as possible. Now, without access to a hospital, and the constant intercourse with other men, the opportunity to follow up one's diagnosis and check and correct it, a G.P. degenerates. He becomes merely a clogged filter. You will almost certainly concede that.

"I have been a G.P. for forty-one years now or more, and during that time I have always had full access to hospitals, operating rooms, labs, x-rays and the post-mortem room. So my work has been interesting and I meet other men, many, if not most of them, better than myself. We discuss cases, see them together, exchange knowledge, etc. That has always been the way here, and I am open to a small bet that most of the G.P.s here are amazingly competent. Many of us do a certain amount of surgery. I have always done most of my own. I don't try work that obviously a specialist should do; but I have a liking for surgery, and through the years have acquired a certain limited dexterity. Surgery, by which I mean operating, is merely a technical skill anyway, and I see specialists doing operations at times, not any less fumblingly than some of the G.P.s. But what I am trying to get at is that if you want to have a large number of competent G.P.s—and they are the first line of defence—you must give them hospital facilities.

"Then there is this point: we have here, at any rate, scores of men who have certificates in surgery, gynæcology and what-not, doing general practice all the time. It would be quite unfair and dishonest for them to call themselves specialists. They hope, or intend, to be someday; meanwhile, *il faut vivre*.

"And lastly, the emphasis is, I think, swinging away from specialists to a certain extent. I don't mind saying here that I think the modern way of taking interns *ab ovo*, or rather still *in ovo*, and making them into surgeons, or eye men, or g.u. men, and so on, is entirely wrong. How does a man in his fourth or intern year know that ultimately he wouldn't be better in some other specialty? And what about his contact with human beings? A sick man or woman is not case 116 or 118; it is Mr. Robert Jones, who overeats and doesn't take exercise, and has business worries, and a wife who nags him; or it's Mrs. Sadie Brown, who has too many children, and not enough money, and has no holidays, and flat feet. The G.P. has to know all these things; the specialist neither knows nor cares; and so he doesn't help the patient as much as he should. Only through general practice can he learn. And so I rejoice that so many highly certificated younger men have to go through the mill of general practice. I think every man should; not because I'm a G.P., but because I know from forty-one years' experience that the most useful specialists I have known have been men that have been G.P.'s first, that gradually discovered what they were best at, and liked best, and then limited their practice. And no amount of tosh talked by specialists will ever convince me otherwise. We all tend to forget that medicine is, or should be, a *healing* art, and healing means a lot more than the application of techniques, be the application never so skilful.

"When we talk about health insurance or a wider availability of medical care, we should not be thinking merely of specialist care. What is needed is more general care. Now this throws a responsibility on us G.P.'s. We are by no means all white, nor the specialists all black. The latter have their stones to throw, too. If we are going to organize as a group, and demand this and that, we must show our good faith by making ourselves better G.P.'s, doing better office examinations, making better diagnoses, calling in consultants and specialists more frequently and readily, and both sides must be willing to work together all the time."

*This was a comment re the General Practitioner Section. —EDITOR.

Members are reminded to make early application for accommodation at Banff for the Annual Meeting in June, 1952. The form of application has appeared in November and December, 1951 issues, and separate forms may be had from the General Secretary's office, 135 St. Clair Ave. W., Toronto.

MISCELLANY

COMMENTS ON MEDICAL EDUCATION

[*The following editorial is taken from the "Bulletin of the Vancouver Medical Association," October, 1951. It deals with aspects of our professional life which are as familiar as they are insistent, perhaps* because *they are so insistent, and handles them with a masterly recognition of their importance.*—EDITOR.]

WE WERE GREATLY INTERESTED in the speech of Dr. H. B. Church, the President of the Canadian Medical Association, made recently, in which he deplores the tendency on the part of the medical student to think only in terms of specialism when he graduates, or as soon as possible, rather than of taking up general practice. He laments, too, the fact that the general practitioner, and particularly the country doctor, is so lightly regarded, and is becoming the "forgotten man" of medicine.

Those of us now in the sere and yellow, or at least rapidly approaching that unattractive stage of our careers, will sympathize a great deal with Dr. Church, and there is much in what he says. It is true that the "family doctor", who, in his way has played so important a part in medical practice, is becoming scarcer all the time. But we cannot back the clock. In the words of the poet,

"Oh world where all things change and naught abides
Where e'en though better follow, good must pass . . ."

There are many reasons why the trend is becoming so definitely set towards specialism. With all due deference to Dr. Church, if he is reported correctly, we do not believe it is mainly a mercenary instinct that makes the young medical student, about to graduate, decide to specialize early. There may be some element of attraction in the supposedly higher financial reward of specialism; but things tend to level out, and in any case, Mr. Abbott is always there to see that the specialist, no less than the general practitioner, shall have "his bounds set, that he may not pass", in the matter of income.

We think, as we observe the young entry, that they are a very good lot—at least as good as we were when we graduated, though perhaps not as resigned to hard work, and not quite so ready to accept night calls, and unassisted maternity work. They are less willing, too, to take up country work, and cling to city life. But the type that we see passing through the hospital looks to us like a very fine one; keen, intelligent and full of ardour. The future of medicine is, we think, quite safe in their hands.

Our theory of the "fons et origo mali" is a little different from that of Dr. Church. We cannot help thinking that there are some serious dangers in the modern system of medical training, which puts too much emphasis on specialism from the start, and conditions its graduates in this direction, urging them into specialism. Perhaps this is an overstatement, but it is the impression we have. General practice, which is undoubtedly the best training ground that a man can have, is apparently rather sniffed at.

We regard, too, as wholly pernicious, the system that makes it necessary for a man to secure certification before he starts practice, and makes it practically impossible for a man who has been in practice for several years to come back and secure a specialist's certificate. Yet the history of medicine in Canada until the past few years has shown that nearly all our best specialists came to their full growth in specialism through and after general practice—and we do not accept the theory that modern medicine is so complicated that it cannot continue to be this way.

This system has many bad points. It puts a premium on the financial competence of the student, and not necessarily on true ability. The cost of the extra training is so high that many men who would amply justify having it simply cannot afford it. It shuts out, as we have said, the man who, after several years of practice, has found the department of work that he likes, and at which he is specially good. Again, it forces young men into special fields that in later years, they may discover are not really the fields in which they will be happiest, and most likely to succeed.

We see scores of men who have certificates, to acquire which they have spent many years and much money, forced to take up general practice in order to earn a living. This is very good for them, of course, and fills the ranks of general practitioners, but surely it would have been better for them, if they had been trained on broader lines, to be excellent general practitioners, with the prospect always before them, as it was before the Gallies and the Shepherds, and the Howards and Gordons and all the other giants of our profession, who, like Jacob of old, were content to serve their seven or fourteen years, so that they could in the end, get the Sarah for whom they had toiled, in the form of the specialty they wanted and for which they had fitted themselves.

We can only hope that some day the pendulum will swing back (it generally does) and a truer and better system will be found, where men will begin, as we think they should, in general practice, and gradually climb up to the higher levels of specialism. And then the country doctor will come into his own again, for there was never any more fertile source of good specialists than these country practitioners, who have learnt their art literally from the grass roots up, and who were given the opportunity of advancement rightfully theirs, in the days when things were allowed to follow a natural, rather than an artificial, course of development.

CORRESPONDENCE

THE PRINCESS TSAHAI MEMORIAL HOSPITAL IN ETHIOPIA

To the Editor:

Canada and the Canadians has shown so warm and friendly an interest in Ethiopia; so many Canadians have held positions there under the Ethiopian Government, that I venture to make through your *Journal* an appeal on behalf of a project which I feel will have the sympathy and support of your readers.

I am sure they will remember the sad plight of Ethiopia in 1935 when she was invaded by the forces of Mussolini, powerfully equipped with modern arms against which she had no adequate defence. At the time the heroic courage of the young Princess Tsahai, The Emperor's daughter, then only 16 years of age, was outstanding. Her eloquent broadcast appeal against the use of poison gas was heard in London. In Addis Ababa she organized the Ethiopian Women's Work Association, and led her compatriots in the manufacture of gas masks, bandages and comforts for the troops. On arrival as an exile in London she entered the Children's Hospital at Great Ormond Street where, after three years' devoted service, she qualified as a State Registered Nurse. She then proceeded to Guy's Hospital for post-registration training. She was at Guy's during the great air raids when she displayed both courage and a capacity for leadership.

On returning to Ethiopia with a unit of British Red Cross Nurses, she performed a great task in establishing an orphanage for children whose parents had been killed in the war, and in opening numerous hospitals and clinics. Most tragically she did more than her strength allowed. She died suddenly in a remote province for lack of the skilled aid she was endeavouring to bring to others.

It was felt by those in Britain who realized the great loss that the death of this young Princess would mean to her country, that a Memorial Hospital should be raised in Ethiopia to continue her own great efforts. The formation of the Princess Tsahai Memorial Hospital Council in London was gratefully welcomed by Their Imperial Majesties, The Emperor and Empress, who graciously consented to become Patrons of the Hospital. The Archbishops of Canterbury and York, leaders of other Churches, and the Ambassadors of the United Nations consented to be Honorary Presidents: leaders of the medical profession, universities and schools, with prominent social workers, accepted the office of Vice-Presidents. Upwards of £50,000 was raised for the project in this country, and a similar sum in Ethiopia itself. Her Majesty, The Queen, graciously honoured the Fund by a donation of £100.

The Hospital is now complete and the official opening took place on November 2, Colonel W. Byam, for twenty-five years Lecturer on Tropical diseases at St. George's Hospital London, and with Sir Robert Archibald, Editor of "Practice of Medicine in the Tropics", has accepted the position of Director of the Hospital.

Further financial support is urgently needed. The Memorial Hospital Council in London requires a further £1,500 to pay for goods already sent to Addis Ababa: moreover, still further equipment is required, for the Pharmacy and Laboratory in particular—both of which are vital.

The Princess Tsahai Memorial Hospital is destined to be of immense importance to Ethiopia in the training of nurses and, subsequently, of physicians and surgeons, in co-operation with the new University College and its Canadian director. Special attention to research into the treatment of tropical diseases will be given under the auspices of Colonel Byam who has made this his life study. Such research will be valuable to all who live in all the tropics. Ethiopia is in the unique position, owing to the various altitudes and their respective climates, of affording opportunities for the study of all the tropical diseases.

The Hon. Treasurers, both leaders of the medical profession, will most gratefully acknowledge all donations to the Fund. Cheques and Money Orders should be drawn in favour of Princess Tsahai Memorial Hospital, and addressed to Lords Horder, G.C.V.O., M.D., and Amulree, M.D., F.R.C.P., M.A., c/o Messrs. Gould and Prideaux, 88 Bishopsgate, London, E.C.2., through any branch of Barclays Bank—Colonial, Dominion or Overseas.

E. SYLVIA PANKHURST,
Hon. Secretary.

SPECIAL CORRESPONDENCE

The London Letter

(From our own correspondent)

THE KING

The Services of Thanksgiving which were held in churches of all denominations throughout the length and breadth of the land on December 9, for the King's restoration to health marked the end of a period of deep anxiety on the part of all His Majesty's subjects. It was on September 23 that the King underwent an operation for resection of the lung. The subsequent bulletins indicated an uneventful postoperative period, and the later progress has been eminently satisfactory. The burden of responsibility resting upon the shoulders of the Royal medical advisors, and particularly the thoracic surgeon who performed the operation, has been a heavy one, and there has been nothing but praise for the skill and equanimity with which they have fulfilled their task. An operation of this type in a middle-aged patient is always a formidable task, and the rapid recovery of the King is a notable tribute to the skill and ability of the operating surgeon and his team. The prayers of thanksgiving on December 9 were linked with His Majesty's subjects' loyal and sincere hopes that the final stage of convalescence would restore the King to a long period of renewed health.

THE NEW MINISTER OF HEALTH

Captain H. F. C. Crookshank, the new Minister of Health, made his first public speech as Minister of Health, at the British Medical Association Dinner last month. A large audience, representative of all sections of the profession, gave him a warm welcome, and there was no doubt as to the favourable impression he created. There were no fireworks—elocutionary or otherwise—but a straightforward brief outline of how he proposed to approach the task. He was the son of a doctor and therefore felt that he knew something about the profession. "We must be friends. It takes two to make a quarrel, and I do not think that either of us wants to quarrel." A good politician had to keep a balance between the obviously desirable and the practically possible. By co-operation between the Ministry and the profession the people of the country could be assured an efficient Service. Differences of opinion there are bound to be, but there can be no doubt that Captain Crookshank has made an excellent first impression. The only fear that some have is that his onerous duties as Leader of the House of Commons may distract his attention from the Ministry of Health. With mutual co-operation and understanding there is no reason why the efficiency of the Service should not be vastly improved—and at no additional cost to the Treasury.

MEDICAL RESEARCH COUNCIL

The recently published report of the Medical Research Council for the two years ending September 1950 provides an interesting résumé of developments in this field, although its belated appearance detracts from its intrinsic interest. The field covered is a wide one, ranging from the common cold to the biological aspects of atomic physics. Not unnaturally the section on cancer research has attracted most public attention, as the greater part of it is devoted to a review of the work done on the possible relationship between smoking and carcinoma of the lung. This is a problem which has been the subject of somewhat acrimonious controversy in the correspondence columns of the medical press recently. Tobacco, like alcohol, seems to be incapable of discussion in a reasonable atmosphere; both arouse the aggressive instincts of those who do not approve of them. The result is that the press, medical schools, open-minded doctors—all have been accused of plotting to play down and deprecate the statistical reports which have been published on the subject.

An interesting feature of the report is that showing the increased part played by the Department of Biological Standards in the preparation of new standards for the Expert Committee on Biological Standards of the World Health Organization. Thus, in addition to continuing as a world centre for the distribution of 21 international standards, it has made new standards for streptomycin, provitamin A, ACTH, and anti-A and anti-B blood grouping sera. The provisional British standards for dimercaprol (BAL), hyaluronidase and oxophenarsine (a joint Canadian-British standard) were being considered for international adoption at the time the report was written.

London, December, 1951. WILLIAM A. R. THOMSON

Bearing in mind the famous aphorism of Hippocrates that if he can do no good, he should do no harm, the physician should beware of saying too much in a patient's hearing. There are so many people whose minds are poised on the precipice of morbidity that the slightest suggestion hurls them headlong into the abyss.—F. Brodie, *Canad. M. A. J.*, **11**: 240, 1921.

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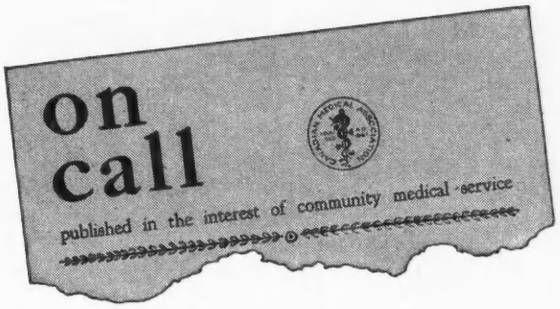

IS THE PROFESSION MISUNDERSTOOD?

IAN MACNEILL

[*For the past two years Mr. Ian MacNeill, whose article appears hereunder, had a very intimate contact with the Canadian Medical Association as our public relations officer, employed by Public & Industrial Relations Limited. Mr. MacNeill has now left to become Assistant to the Commissioner, National Film Board, Ottawa, but has found time to set down in retrospect some of his impressions during his close, and for us at any rate very pleasant relationship with our Association.*—EDITOR.]

For almost two years I have been working in public relations with the Canadian Medical Association. Now that the job will be carried on by my former associates it's been suggested that I step out of the more or less anonymous rôle of the public relations counsel and deliver what might be called a valedictory.

When I was assigned to the C.M.A., part of my job was to bring an objective, outside viewpoint to the affairs of the Association. But, I tackled it with some substantial personal reservations. Though I knew and admired many individual doctors my own attitude towards the organized profession was critical. The medical association, I believed, were the voices of conservatism, not to say reaction. Their chief objective was to maintain the *status quo* in our system of medical care, even at the cost of the country's health. They sometimes protected the inefficient physician and penalized the pioneer. The Canadian doctor must toe their line or face professional ostracism. They were in effect, tight and dictatorial trade unions.

In the past two years, I've discovered how remarkably wrong my early opinions were. I've worked closely, day to day, with the CMA staff. I've met hundreds of the Association's members. I've attended general council meetings, annual meetings, sectional business meetings, committee meetings and division and district meetings. Throughout, my viewpoint remained that of the critic. I believed my job as public relations counsel was as much to represent the public to the profession as to help interpret the doctors to the public. What did I find? An organization rooted in parliamentary traditions, which gives full scope to the rights and opinions of individuals and minorities within it. A group that, contrary to the accusations of politicians and others, has done more to develop a practical approach to the medical care security Canadians want than all other groups combined. And that includes governments. A group that encourages self-criticism and which pays heed to the criticisms of others, a characteristic which is rare among trade and professional groups. That is not to say that organized medicine is without faults. It has its share, but more commonly they are those of the form rather than those of the spirit. They will be corrected, for the spirit of the profession is not static; it possesses the dynamic force which is the essence of progress. I know, now, that Canada's health is in good hands. We will not see, here, a duplication of the development in the United Kingdom which is giving the people almost all they want except good medicine. We will not see, either, a profession that ignores or debases the legitimate needs and desires of the people. Rather, I believe the Canadian profession will give the lead to and seek the participation of people and governments in creating a system of medical care security which is practical, non-political and economically workable and which, above all, will provide good medicine.

But many Canadians, unfortunately, share my earlier opinions of the profession. And it is not among the ill-educated that these views are the strongest. They are held by many who think themselves well-informed; educators, journalists, labour leaders, intellectuals, clergymen, social workers, businessmen and others who influence the thinking of the country. Nor are these views a monopoly of the left. They transect every social and political line. They may be summed up thus: admirable as the work of Canadian doctors (generally) has been in the scientific field, their social performance has been lamentable.

I know, now, that those who hold that opinion —and their views are important to the profesison's future—are wrong. But why do general well-informed people hold opinions that, on the record, are wrong? I believe there are two reasons.

First, much as the profession is doing, outside the field of scientific medicine, it is not doing enough. Canada's history abounds in the names of physicians who also have been leaders in arts and letters, in social service, in politics and in other fields outside medicine. But most of these names date back at least thirty years. Today's emphasis on science in medical education, the rapidity with which specifics for diseases are being discovered, and the staggering job of keeping abreast of medical advances, seems to have narrowed the interests and vision of the profession. More and more, doctors seem to live apart, to think apart and, thus, to be set apart from their fellow citizens. This has robbed the country of an important intellectual and social contribution and the profession of an integrated

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place in the community. In his recent valedictory address, Dr. Norman Gosse, past-president of the CMA, called for a return of the profession to the study of the humanities and for a closer relationship between doctors and the community. It was wise and timely advice. If it is effected, the resulting cross-pollination of ideas and information will bring a new vitality and awareness to the profession's efforts in the social field and win deserved respect for their past efforts from the community.

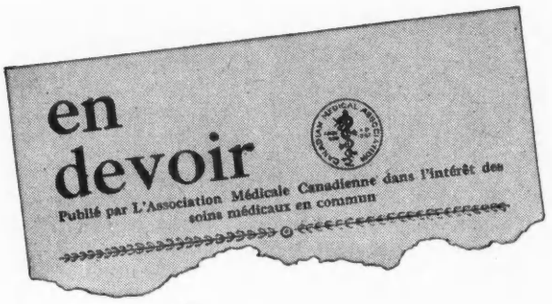
The second factor is a corollary of the first; the feeling, still strong within the profession, that what it does is its own business and no one else's. The profession, often unintentionally, still tends to wrap itself in a cloak of mystery. That may have been fine when medicine and magic were partners. It may have been sound when an intellectual elite ministered to the mental, spiritual and physical needs of the illiterate people. But nominal mass literacy and mass communications have assured that few things, indeed, are private business. Medicine is not one of these. Like education it is too important to the nation's welfare to remain a private preserve. Medicine, whether or not the doctors like it, is now everybody's business. And the profession must accept that, indeed, must encourage it, for the less doctors make a mystery of what they are doing, scientifically and socially, the more understanding and affection they will meet from the public.

A case in point is the profession's attitude towards immigrant physicians. The medical associations have been criticized often and in many forms on this topic. Yet the record tells a story that is overwhelmingly favourable to the profession. It is a story that can be strongly supported by figures and facts yet the public has not been told that story because some sections of the profession believe that it is not the public's business. Since, as a self-governing group, the profession is acting on the public's behalf, it is very much the public's business.

The medical profession can stand up to any scrutiny. Its weaknesses are far out-balanced by its virtues, not the least of which is its sincere desire to correct those weaknesses. The profession can only gain by taking the public into its confidence, by telling people of its hopes, its methods, its successes—and its failures. The profession can only lose by maintaining its reserve.

A rededication to the profession's traditional rôle as a leader in *all* fields of human endeavour, and a frank partnership with the community in that task; these, I believe, should be among its main objectives.

It is not enough to do good; one must do it the right way.—John, Viscount Morley.



LA PROFESSION EST-ELLE MECONNUE?

IAN MACNEILL

[Au cours des deux dernières années, M. Ian MacNeill, dont l'article paraît ci-dessous, a travaillé en relation étroite avec l'Association Médicale Canadienne, à titre d'officiel en relations publiques, employé par Public & Industrial Relations Limited. M. MacNeill nous a maintenant quittés pour devenir assistant-commissaire de l'Office National du Film à Ottawa, mais il a trouvé le temps de faire un retour et de nous présenter ses impressions résultant du contact intime et pour nous, très appréciable, qu'il a eu notre Association.— EDITEUR.]

Pendant près de deux années, je me suis dévoué aux relations publiques de l'Association Médicale Canadienne. Ce travail est maintenant continué par mes anciens collègues, mais il a été suggéré que je fasse un retour plus ou moins désintéressé du rôle de conseiller en relations publiques, pour écrire ce qu'on pourrait appeler une allocution d'adieu.

Lorsque j'ai été nommé au service de l'Association Médicale Canadienne, une part de mon travail consistait à donner un point de vue objectif et extérieur des affaires de l'Association. Au début j'entrepris cette tâche non sans quelques réserves personnelles. Bien que je connaisse et admire plusieurs médecins individuellement, je voyais la profession en général avec un œil critique. Je croyais alors que l'Association Médicale était ancrée dans un esprit de conservation pour ne pas dire réactionnaire. Son premier objectif semblait viser à maintenir son *status quo* dans notre système médical même au prix de la santé publique. Parfois, le médecin incompétent était protégé tandis que le pionnier était puni. A mon avis, le médecin canadien devait suivre la ligne de conduite établie ou faire face à l'ostracisme de la profession. Il s'agissait d'unions rigides et autoritaires.

Au cours des deux dernières années, j'ai découvert jusqu'à quel point mes premières opinions étaient fausses. J'ai travaillé en relations étroites avec le personnel de l'Association Médicale Canadienne, j'ai rencontré des centaines de membres de l'Association et j'ai assisté aux réunions du grand conseil, aux congrès annuels, aux réunions d'affaires de chaque section, aux assemblées des comités et aux sessions tenues

par les divisions et les régions. Pendant toute cette période, mon point de vue a gardé son sens critique et j'ai pensé que mon travail de conseiller en relations publiques consistait autant à présenter les vues du public à la profession, qu'à aider les médecins à se faire connaître aux yeux des gens. Qu'ai-je constaté? Une organisation établie sur des traditions parlementaires qui donnent le champ libre aux droits et aux opinions des individus et des minorités dans son cadre. Un groupe qui, contrairement aux accusations des politiciens et autres, a accompli plus pour développer une approche pratique en faveur des soins médicaux voulus par les canadiens, que tous les autres groupements ensemble y compris les gouvernements. Il s'agit d'un organisme qui encourage la critique à son égard et qui se soucie de cette critique formulée par les autres, ce qui est une caractéristique rare parmi les groupes professionnels et commerciaux. Cela ne veut pas dire que la médecine organisée est dans défauts car elle a aussi sa part; mais ces anomalies se rattachent plutôt à la forme qu'à l'esprit et seront corrigées parce que l'attitude de la profession ne se contente pas d'un état passif. Elle possède cette force dynamique qui est l'essence même du progrès. Je sais maintenant que la santé des Canadiens est entre bonnes mains. Nous ne verrons pas ici une reproduction du développement survenu au Royaume-Uni, qui donne au peuple tout ce qu'il désire excepté de bons soins médicaux. Nous ne verrons pas aussi une profession qui ignore ou amoindrit les besoins et les désirs légitimes du peuple. Je crois plutôt que la profession au Canada sera à la tête d'un mouvement où le peuple et les gouvernants participeront à création d'un système sûr au point de vue médical, et ce système en étant pratique, non-politique et économique, apportera par-dessus tout, un bon service médical.

Malheureusement un grand nombre de Canadiens partagent les premières opinions que j'éprouvais à l'égard de la profession médicale, et c'est parmi les gens même les mieux renseignés que ces idées prévalent, comme les éducateurs, les journalistes, les dirigeants ouvriers, les intellectuels, les membres du clergé, les sociologues, les hommes d'affaires et d'autres dans une position pour influencer la pensée du pays. Ces vues n'appartiennent pas non plus seulement aux partis opposés mais sont partagées dans tous les milieux politiques et sociaux. Nous pouvons en somme résumer ainsi cette attitude: Bien que le travail des médecins canadiens (en général) soit très admirable dans le domaine scientifique, leur présentation au point de vue social est lamentable.

Je sais maintenant que ceux qui partagent cette opinion, et celle-ci est importante à l'égard de l'avenir de la professon, sont dans l'erreur. Mais comment se fait-il que des personnes généralement bien renseignées possèdent ainsi des idées fausses? A mon avis, il y a deux raisons.

Premièrement, en dépit du travail accompli par la profession en dehors du domaine scientifique, la mesure n'est pas suffisante. L'histoire du Canada abondent en noms de médecins qui se distinguèrent dans les arts et les lettres, dans le service social, dans la politique et autres activités en dehors de la médecine. Mais la plupart de ces noms remontent à plus de trente ans. De nos jours, la mise en valeur de la science elle-même dans les études médicales, la rapidité des découvertes relatives à certaines maladies, et le travail immense qui est demandé pour suivre les développements de la science, semblent avoir restreint les intérêts et les activités de la profession. De plus en plus les médecins semblent vivre à part, penser à part et ainsi évoluer dans une sphère différente de celle de leurs concitoyens. Ces faits ont privé le pays d'une importante contribution intellectuelle et sociale, ont empêché la profession d'occuper une position intégrante dans la société. Au cours de son récent discours d'adieu, le Dr Norman Gosse, ancien président de l'AMC, demandait un retour de la profession aux humanités et une relation plus étroite entre les médecins et la société. Ce conseil est sage et arrive au bon moment. S'il se réalise, il en résultera un mariage d'idées et de renseignements qui apporteront une nouvelle vitalité et une plus grande valeur aux efforts de la profession dans le domaine social, ce qui gagnera le respect de la société pour le travail accompli par les médecins dans le passé.

La seconde raison est corollaire à la première. Il existe un sentiment au sein de la profession même, qui lui fait se confiner dans ses propres affaires sous l'idée que les autres n'ont pas besoin de les savoir. La profession, souvent sans le vouloir, a tendance à se renfermer dans une tour d'ivoire. Cette attitude était peut-être justifiable au temps ou la médecine et la magie étaient alliées, et elle était même acceptable aussi lorsqu'une élite intellectuelle se dévouait aux besoins moraux, spirituels et physiques des gens illettrés. Mais l'éducation générale du peuple et les communications plus étendues ont diminué les domaines où les affaires sont demeurées privées. La médecine est l'un de ces cas. Comme l'instruction, elle est trop importante au bien-être de la nation pour demeurer un domaine privé. La médecine, que les médecins le veulent ou non, est maintenant la préoccupation de tout le monde. La profession doit accepter ce fait, l'encourager même, et moins les médecins rendront mystérieuses leurs activités scientifiques et sociales, plus ils seront compris et appréciés par le public.

Un cas à remarquer est l'attitude de la profession à l'égard des médecins immigrants. L'Association a souvent été critiquée sous plusieurs formes à ce sujet. Pourtant les faits démontrent une situation qui est excessivement favorable à la profession. Il s'agit de faits qui peuvent être soutenus par des chiffres et des résultats et pourtant le public n'a pas été mis au courant parce que certaines sections de la profession

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croient que ces affaires ne concernent pas le public. En tant que groupement autonome, la profession agit au nom des gens et ceux-ci ont le droit de connaître les faits.

La profession médicale est en mesure de subir toute enquête à son sujet. Ses faiblesses sont beaucoup compensées par ses vertues et l'une de ces dernières qui mérite notre considération est le fait que la profession démontre un désir sincère de corriger ses défauts. La profession ne peut que gagner davantage en mettant le public au courant de ses confidences, en communiquant aux gens ses espoirs, ses méthodes, ses succès et même ses insuccès. La profession peut y perdre seulement si elle maintient sa réserve.

Il faudrait un retour du rôle traditionnel de la profession comme dirigeant dans tous les domaines de l'activité humaine et comme franc partisan avec la société, pour accomplir les devoirs humanitaires qui s'imposent. Cette réalisation, à mon avis, devrait compter parmi les objectifs importants de la profession.

OBITUARIES

DR. J. A. ALLARD, of Bromptonville, Que., died in St. Vincent de Paul Hospital, Sherbrooke, on November 8 after a lengthy illness. He was in his 77th year.

Dr. Allard, who had practised medicine for the past 52 years, was a former mayor of Bromptonville, and a well known doctor throughout the Eastern Townships of Quebec. He took a keen interest in politics and in the social and welfare work of the community. He is survived by his widow, a son and two adopted daughters.

DR. JOSEPH ALBERT BERGERON, died suddenly on October 23 while on his way to his office. He was 65 years of age. Dr. Bergeron had been practising in Mattawa since 1912. During his career, he held various public offices including those of district coroner, government health officer, Separate School Trustee and Canadian Pacific Railway physician.

A native of St. Antoine de Tilly, Que., he studied at Levis College and graduated from Laval University Faculty of Medicine in 1912. He leaves his widow and three daughters.

DR. A. MELVILLE CAMPBELL, aged 50, a medical practitioner in Toronto for over 22 years died on November 10 at his home. Dr. Campbell was born in Toronto and was a graduate of the Faculty of Medicine of the University of Toronto. Following his graduation he had taken postgraduate study in the United States. He leaves his widow, three sons and two daughters.

DR. JOHN GRANT GUNN, prominent medical practitioner in London, Ont. and former staff member of Westminster Hospital, died on October 27 in Westminster Hospital after a two-month illness. He was 76. Well known in Ontario medical circles, Dr. Gunn was noted for his athletic ability when a young man. A veteran of two wars, he served in the South African War and went overseas as a major with the Canadian Medical Corps during the First World War.

Born at Brechen, Dr. Gunn graduated in medicine from the University of Western Ontario in 1904. He was a member of the Canadian Medical Association, the Ontario Medical Association and the Masonic Lodge. Beside his widow, he is survived by one son.

DR. G. M. HATFIELD, for many years a general practitioner in Halifax, died in French Village on November 9. Born in Yarmouth, he was a graduate of Dalhousie University, and took postgraduate work in Montreal and Chicago. He did general practice work in Yarmouth before moving to Halifax some years ago. He leaves his widow.

DR. HANS HERSCHMANN, aged 76, died suddenly at Misericordia Hospital, Winnipeg, on November 4. Graduing M.D. from Vienna in 1903, he practised at Fort Frances, Ontario, and in Winnipeg for the past 50 years. He became a member of the College of Physicians and Surgeons, Manitoba, in 1908. Last year he retired from practice.

DR. W. S. HUNT, one of Sarnia's best known specialists, died on October 16 at the Mayo Clinic, Rochester, Minnesota, following an operation. He was 69 years of age. Born in London, Ont., he attended London schools and went to the University of Toronto. After graduating he specialized in eye, ear, nose and throat diseases. He is survived by his widow, one son and one daughter.

DR. RICHARD WELLINGTON KENNY, aged 72, of Winnipeg, died on October 24. Born in Ottawa, he was an honour graduate in medicine from McGill University, and took postgraduate study in New York. He moved to Winnipeg in 1905. During the first world war Dr. Kenny served as medical officer with the 10th battalion, C.A.M.C., and was awarded the Military Cross. He was a medical officer with the R.C.M.P. from 1920 to 1947, and was a surgeon with the Canadian Pacific railway from 1919 to 1944. Surviving are two daughters.

DR. DONALD S. McEACHERN, died suddenly in Montreal on October 31, aged 47. Dr. McEachern was senior neurologist and chief of the neurological service of the Montreal Neurological Institute, associate professor of neurology at McGill University and neurologist to the Royal Victoria Hospital. He was born in Toronto. He graduated with honours from the University of Manitoba in 1926, and was at the Winnipeg General Hospital, the Presbyterian Hospital of New York and Johns Hopkins Hospital, Baltimore, where he became Jacques Loeb Fellow in Medicine in 1928-30. Dr. McEachern came to the Neurological Institute in 1936 after study at Queen's Square Hospital for Nervous Diseases, London. He served with the Royal Canadian Army Medical Corps from 1942 to 1945 with the rank of Lieut.-Colonel. After the war he became chief consultant in neurology at Queen Mary Veterans' Hospital. His widow, a son and a daughter survive him.

AN APPRECIATION

News of the death on October 31 of Dr. Donald McEachern of Montreal at the age of 47 awakened many memories in the minds of western readers. "Whom the Gods love, die young", is true of this gifted friendly soul who moved among us for so short a time. "Lycidas is dead, dead ere his prime", yet already he had achieved great things in his chosen field. President of the Canadian Neurological Society, chief of the neurological service of the Montreal Neurological Institute, associate professor of neurology at McGill University and Neurologist to the Royal Victoria Hospital: these are no mean honours for a comparatively young man.

He had many links with Winnipeg and the Canadian west. Coming from Toronto with his parents, he graduated with honours from the University of Manitoba in 1926. As an intern in the Winnipeg General Hospital he organized an active Osler Society. His father was responsible for having the addresses delivered before the Society in 1926-27 put into book form and a copy of this is among the prized possessions of the writer.

Donald McEachern married Miss Corinne Irwin, a grand-daughter of Dr. F. B. DuVal, the well-beloved pastor of Knox Church, Winnipeg. His brother John is a prominent cardiologist of Winnipeg where two of his

sisters, Mrs. Edward Nanton and Miss Betty McEachern also live. Another sister, Mrs. F. Gwyn, lives in Moose Jaw. Our sympathy goes out to them and to his widow and the two children, Gail and John.

Donald's spirit of public service derived in part at least from his father, the late John McEachern, western supervisor of the Bank of Montreal, who for many years was chairman and guiding spirit of the Manitoba Sanatorium Board.

One may compare Donald McEachern with the two heroes of Canadian medicine, Sir William Osler and Sir Frederick Banting, in devotion to science, range of interests, charm of manner and fineness of character.

Ave atque vale! ROSS MITCHELL

DR. ALBERT E. MACAULAY died in Owen Sound October 27, after a long illness. Dr. Macaulay was born in Saint John 65 years ago. He graduated from McGill in 1920 and interned in the Royal Victoria Hospital. He did postgraduate study in surgery in London, Edinburgh, Paris and Vienna and regularly visited surgical centres in the U.S.A. He was a fellow of the American College of Surgery. He was in turn superintendant of the Saint John General Hospital, attending surgeon and surgeon in chief of his home hospital. As a surgeon he had exceptional mechanical skill and a delicate touch in handling tissue which was reflected in his surgical success. He held office in the Saint John Medical Society, N.B. Medical Society and represented New Brunswick on the executive of the C.M.A. He was a keen yachtsman specializing in power boats. He was kindly and hospitality was one of his outstanding qualities. He is survived by his widow and two daughters.

DR. WILLIAM ALEXANDER McFALL, aged 74, who practiced medicine in Toronto for 44 years, died on October 10. Born in Kleinburg, he was educated at Bolton, Harbord Collegiate, and the University of Toronto, graduating in 1899 with the degree of M.B. He took postgraduate study in Philadelphia.

Until he returned to Toronto in 1907, Dr. McFall practised in Peterboro. In 1949 the University of Toronto conferred an M.D. degree on completion of 50 years' practice. Dr. McFall had a hobby of studying place names and had written a number of articles on the migration of place names from the old world to America. He was a member of the Ontario Medical Association, the University of Toronto Alumni. He leaves his widow.

DR. MERLE PATTERSON, Canadian woman doctor serving under the Woman's Missionary Society of the United Church of Canada in Neemuch, Central India, died on October 27, according to word just received here. Her death followed a motor accident while returning from the annual meeting of the Mission Council at Rasulpura. Dr. Patterson's home was in Winnipeg and was a 1942 graduate in medicine of the University of Manitoba. She served internships in Winnipeg and Regina and did postgraduate work at St. Michael's Hospital, Toronto. Dr. Patterson had rendered outstanding service not only to the hospital but to the community as a whole. When a United Church delegation visited Banswara during her term of service, prominent Moslem and Hindu representatives asked to meet them to thank the church for her services to the community.

DR. THOMAS WELLINGTON SUTHERLAND died in Vancouver General Hospital on October 19, following a brief illness. The late Dr. Sutherland was born in Embro, Ont. in 1885. He attended school at Embro and Woodstock. He graduated from McGill, class of 1912. He interned in the Montreal General and Montreal Maternity Hospitals. For a time on graduation he was attached to the Provincial Department of Health in Regina. In 1916 he enlisted in No. 8 Stationary Hospital and saw service in England and France. On returning from Overseas he commenced private practice in Shellbrook, Sask., later having practices at Revelstoke and Parksville in B.C. During the Second World War he served for two years as O.C. of Military Hospitals in Prince Rupert and Gordon Head. He leaves his widow, two daughters, and one son.

DR. JOSEPH H. SPEERS who had a large practice in Toronto died on November 3 at his home. He had been in failing health for some time. Dr. Speers had been practising since 1907. Born at Ivy, Simcoe Township, he attended Barrie Collegiate. After graduating from the University of Toronto, he established a practice in Bracebridge, leaving there to come to Toronto in 1916. He was a life member of the Academy of Medicine. He leaves his widow, a daughter, and a son.

DR. JOSEPH CHARLES WOODS died in hospital on November 17, 1951. He was in his 65th year.

Born at Aylmer, Quebec, he received the degree of Bachelor of Arts from Laval in 1908 and three years later his medical degree. From 1929 to 1935 he was president of the staff of the Ottawa General Hospital and from 1936 to 1945 was surgeon general. Then he became a member of the advisory board and consulting surgeon. For 10 years he had been in charge of the old Misericordia Hospital, now St. Vincent's Hospital. A Fellow of the American College of Surgeons, he held membership in the Ottawa Academy of Medicine, the Canadian and the Ontario Medical Associations, also the French-Speaking Doctors of Canada, Ottawa Medical Society and the French-Canadian Institute of Ottawa. He was predeceased by his wife in 1949. Survivors are four sons, four daughters, and three sisters.

A friend has said of him: "He was one of God's gentlemen".

ABSTRACTS *from current literature*

MEDICINE

Value of Gastric Biopsy in the Study of Chronic Gastritis and Pernicious Anæmia.

WOOD, I. J.: BRIT. M. J., 2: 823, 1951.

The author has perfected a snare-type flexible gastric biopsy tube. The fragment of gastric mucosa is most frequently removed from the greater curvature of the body of the stomach. There has been no evidence of perforation or ulceration in 552 biopsies. Hæmorrhage (hæmatemesis and melæna) has occurred in 6 cases. Hæmorrhage in the biopsy fragment is common in superficial gastritis, and this may lead to recurrent gastric bleeding of a minor degree. Atrophic gastritis appears to be a more advanced stage of superficial gastritis, with an atrophy of the acid- and pepsin-secreting cells as well as the inflammatory reaction. There is little or no evidence of the association of pernicious anæmia or subacute combined degeneration of the spinal cord with atrophic gastritis. In pernicious anæmia there is marked atrophy of the gastric mucosa with a tendency to intestinal metaplasia; no inflammatory changes; the mucosa shows no tendency to regenerate when given standard liver therapy over a period of years; the mucosa does not regenerate with biweekly injections of vitamin B_{12}. This type of lesion has been termed gastric atrophy. The author postulates that if gastric atrophy could be arrested or prevented so too would pernicious anæmia and subacute combined degeneration of the spinal cord.

J. A. STEWART DORRANCE

Abacterial Cystitis.

CZEKALOWSKI, J. W. AND HORNE, G. O.: BRIT. M. J., 2: 879, 1951.

Abacterial cystitis is a syndrome of the signs and symptoms of cystitis but no organisms are demonstrated in the urine; there is no constitutional upset, but there are severe local symptoms with dysuria, frequency, and

sometimes terminal hæmaturia. Cystoscopy reveals an intense cystitis with marked reduction in the capacity of the bladder; pyelography may show slight dilatation of the ureters and renal pelves. There is heavy pyuria with red blood cells, but no organisms may be seen or cultured in the centrifuged deposit, using the routine culture media. Most chemotherapeutic and antibiotic agents have little or no effect. Neoarsphenamine always causes a dramatic response and rapid cure, regardless of the duration of symptoms. The pyuria clears up; the capacity and mucosa of the bladder, the ureters and renal pelves return to normal. The causative organism may be a spirochæte. The authors report on 3 cases in which spirochætes were demonstrated on dark-ground examination, although no organisms were grown from mid-stream specimens of urine. It is emphasized that there is no definite proof that spirochætes cause this syndrome. J. A. STEWART DORRANCE

The Effect of Hæmoglobin on Renal Function in the Human.

MILLER, J. H. AND MCDONAL, R. K.: J. CLIN. INVESTIGATION, 30: 1033, 1951.

Anuria, oliguria, and renal failure are frequently associated with hæmoglobinuria. The mechanism of renal failure associated with hæmoglobinuria has not been demonstrated, nor has the adverse effect of hæmoglobin been established on the human kidney. The authors performed 36 renal clearance tests on 25 men before and after the administration of hæmoglobin, intravenously in doses up to 15 gm. Autogenous autolysed blood preparations or commercially prepared hæmoglobin caused prompt physiological changes; diastolic and systolic blood pressures were elevated; the pulse pressure increased as the pulse rate fell; the clearance of inulin and PAH decreased; the filtration fraction increased; the urine flow decreased; and the glomerular filtrate reabsorbed by the renal tubules increased. Follow-up studies 24 to 48 hours after the injection of hæmoglobin showed a return to normal of the renal clearances. Extracorpuscular hæmoglobin may induce renal vasoconstriction while the injection of hæmoglobin (intracorpuscular) causes no changes in renal physiology. J. A. STEWART DORRANCE

Electrolyte Equilibrium During Mercurial Diuresis.

SCHWARTZ, W. B. AND WALLACE, W. M.: J. CLIN. INVESTIGATION, 30: 1089, 1951.

Ten patients in congestive heart failure received 2.0 ml. of mercuhydrin, intramuscularly, at the beginning of each day of study. Each interruption of treatment was followed by a cessation of the loss of body water and electrolyte. Electrolytes and water were lost causing a chloride depletion associated with alkalosis without changes in the concentration of serum sodium. This was associated with a loss of intracellular fluid and potassium with a reduction of serum potassium concentration. When this occurred there was no diuretic response to the mercurial; when the chloride deficit was restored to normal by ammonium chloride or dilute hydrochloric acid response to the mercurial was restored. When chloride excretion was greater than sodium excretion the chloride surplus was covered by potassium and ammonium. The usual renal response to mercurial diuretics may result from interference with tubular reabsorption of chloride and the loss of fixed cation is secondary to the effect on anion excretion. J. A. STEWART DORRANCE

The Effects of Hypertonic Glucose on Metabolism of Water and Electrolytes in Patients with Œdema.

TARAIL, R., SELDIN, D. W. AND GOODYER, A. V. N.: J. CLIN. INVESTIGATION, 30: 1111, 1951.

Rapid injection of hypertonic glucose causes marked hypoglycæmia in normal humans, this raises the osmotic pressure of the extracellular fluid and withdraws water from cells causing an expansion of the extracellular volume and depressing the concentration of serum sodium. Patients with cardiac œdema (3) and œdema due to hepatic cirrhosis (4) were given 600 to 1,200 ml. of 25% glucose intravenously in 30 to 90 minutes. The urine flow was increased but water losses were not greater than the volume of fluid injected. During the period of hyperglycæmia sodium, potassium, phosphorus, and chloride were excreted in excess of normal and then returned to normal levels. The sodium depots were slightly depleted during the period of sodium diuresis. Severe muscular cramps occurred in those patients who were not given supplemental intakes of water while the glucose was being administered. The conclusions from this study are that glucose is of little value in the treatment of intractable œdema. J. A. STEWART DORRANCE

Treatment of Chronic Otorrhœa, with Chloramphenicol.

LEWIS, R. S. AND GRAY, J. D.: BRIT, M. J., 2: 939, 1951.

Chronic otitis media, chronic otitis externa, and infection of the cavities made by tympano-mastoidectomies and fenestration operations cause persistent otorrhœa in 1 to 3% of the population. There are 2 groups—the "safe" and the "dangerous". The "safe" ears are those in which the complications threatening life practically never occur, since the infection is limited to the lining mucous membrane; but the pathological changes in the middle ear and mastoid process in the "dangerous" group cause bone destruction, which may lead to fatal intracranial complications. "Dangerous" ears include all cases with an attic or posterior marginal perforation. "Safe" ears include inferior and marginal perforations. Wicks soaked in a 15% solution of chloramphenicol in propylene glycol giving a concentration of 150,000 μgm./ml. were inserted into the affected ears for 48 hours. At this concentration chloramphenicol is a bactericide, and causes the ears to become dry in 82.5% of cases within 7 days. The cotton-wool wicks are preferred to gauze because they hold more solution and do not become detached nor are lost in the ear canal. Volume for volume the solution used for the treatment is six times more concentrated than any used previously. The point of primary importance is that the concentration should be such that the antibiotic available at the periphery of any cavity will overwhelm the organisms. If the amount of chloramphenicol in a solution is too critical there may be insufficient in the hidden recesses of the area under treatment to be effective, or, worse, resistant types of bacteria may be bred. J. A. STEWART DORRANCE

The Medical Treatment of Ulcerative Colitis.

BARGEN, J. A.: POSTGRAD. MED., 10: 317, 1951.

The management of ulcerative colitis depends upon the severity of the illness of the patient. The anxiety of the patient must be overcome as well as his nervous tension. In 20% of cases the disease involves the distal segments of the large intestine, most of these patients, when following a well ordered program, will recover. After recovery the patient must avoid infections of the upper respiratory tract and avoid over-exertion. A patient with ulcerative colitis must live moderately once the disease has been controlled. The most severely ill patient will recover as long as he adheres to his medical regimen. Rarely is surgical intervention necessary and this is only to control a massive uncontrollable intestinal hæmorrhage or localized perforation. J. A. STEWART DORRANCE

Carbon-Dioxide Intoxication in Emphysema: Emergency Treatment by Artificial Pneumoperitoneum.

CALLAWAY, J. J. AND MCKUSICK, V. A.: NEW ENGLAND J. MED., 245: 9, 1951.

Administration of oxygen in chronic anoxæmia usually causes an elevation of the carbon-dioxide content and combining power of the blood. Such elevation may be of profound degree in patients with marked pulmonary emphysema and fibrosis, giving rise to the syndrome of carbon-dioxide intoxication (headache, cutaneous vasodilatation, irrationality, stupefaction and coma). Two such cases are described, the first ending fatally. In the second patient, after seventy-two hours of profound coma, artificial pneumoperitoneum was immediately effective in restoring normal mental function and causing a return to normal of the elevated carbon-dioxide combining power and the depressed serum chlorides. The rapidly beneficial effects of the pneumoperitoneum were considered due to the elevation of the diaphragm to a more efficient working position and of a return towards normal of the ratio of residual air to total lung volume.

NORMAN S. SKINNER

The Influence of Position on the Breath Sounds.

KERR, A.: NEW ENGLAND J. MED., 245: 58, 1951.

The author studied the variations in breath sounds on auscultation of the chest with changing positions in 58 subjects, of whom 39 were normal, 11 had pulmonary disease and 8 had enlarged hearts. The lateral position was found to increase the pitch and intensity on the dependent side of the chest and to decrease both phases on the upper side. It is concluded that auscultatory findings should be interpreted with caution when the patient is not in the upright position. NORMAN S. SKINNER

Gastroscopic Biopsy in the Differential Diagnosis of Gastritis and Carcinoma.

BENEDICT, E. B.: NEW ENGLAND J. MED., 245: 203, 1951.

The Benedict flexible operating gastroscope, introduced in 1948, permits the taking of biopsy specimens from the gastric mucosa. This is of great importance in the differentiation between benign and malignant lesions and is a safe procedure, as evidenced by the experience of the Massachusetts General Hospital Endoscopy Clinic where 203 biopsies of the stomach have been taken without accident or complication. Additional advantages in the use of this instrument are the ability to inflate and deflate the stomach readily and to aspirate gastric secretions for sytologic examination.

Ten illustrative case reports are presented.

NORMAN S. SKINNER

Treatment of Incapacitated Euthyroid Cardiac Patients by Producing Hypothyroidism with Radioactive Iodine.

BLUMGART, H. L., FREEBERG, A. S. AND KURLAND, G. S.: NEW ENGLAND J. MED., 245: 83, 1951.

Hypothyroidism, induced by the administration of radioactive iodine, has been employed as a therapeutic measure by the authors in a group of 37 chronically incapacitated cardiac patients. One third of the group were markedly improved, another third showed definite improvement and in the remaining third no worthwhile benefit was evident. No serious reactions were encountered from the radioactive iodine which induced a mild transitory hyperthyroidism in two patients and a transitory thyroiditis in approximately two-thirds of the group. Myxœdema becomes evident five weeks to six months after the use of the radioactive iodine and it is then necessary to administer small doses of thyroid and attempt to maintain the lowest metabolic rate consistent with the comfort of the patient.

NORMAN S. SKINNER

SURGERY

The Treatment of Oral Cancer by a Combination of Radiotherapy and Surgery.

WOOKEY, H., ASH, C., WELSH, W. K. AND MUSTARD, R. A.: *Ann. Surg.*, 134: 529, 1951.

Cases of carcinoma of the lips and mouth seen during the period 1929 to 1945 include 1,128 lip, 342 tongue and 497 lesions of other sites in the oral cavity. It is predominantly a male disease and tends to be local, distant metastases being rare. About 3% had syphilis and these are more resistant to treatment. Leukoplakia is considered to be pre-cancerous.

All cases of oral cancer are seen in the combined clinic (by both radiologists and surgeons and often by dentists) and in all the diagnosis is confirmed by biopsy. Generally the treatment of the primary is considered to be radiologic unless it involves the dental ridge and bone, or unless the lesion has failed to respond to radiation. Invasion of cervical lymph nodes is felt to necessitate a dissection of the neck. Prophylactic resection of the cervical nodes is no longer done for lip cancer, but is justified in tongue and other intra-oral lesions. It is important to eliminate dental or other infections before an operation.

About 5.4% of these cases developed cancer elsewhere. Of lip cases 13% had or developed metastases and 58% survived five years (excluding those untraced or dying of extraneous disease). Cases of carcinoma of the tongue showed 59% lymph node metastases and a gross five year survival of 34%. Other oral carcinoma cases showed 44% lymph node secondaries and a five year survival of 32%. Early diagnosis directly determines prognosis.

BURNS PLEWES

The Bone Bank in Neurosurgery.

ELLIOTT, H. AND SCOTT, H. J.: BRIT. J. SURG., 39: 31, 1951.

A case of head injury with a compound fracture of the skull, laceration of the dura and frontal lobe, involving the orbit, frontal sinus and ethmoid, is described. The loose bone removed at operation was stored in the deep-freeze compartment of the pathology refrigerator and replaced after boiling 12 weeks later. Silver, celluloid, tantalum, acrylic resin, os purum, rib, iliac bone have been used to fill large skull defects but all have disadvantages. Replacement by the patient's own bone seemed very satisfactory in this case. BURNS PLEWES

Tenosynovitis of the Wrist.

ELLIS, M., BRIT. M. J., 2: 777, 1951.

Tenosynovitis of the wrist is "a sausage-shaped swelling on the radial side of the lower part of the forearm. This swelling is always on the dorsal surface and is always about 1½ inch (3.8 cm.) long, and appears to be slightly oblique to the long axis of the forearm. The lower limit of this swelling never extends distally beyond a point 2 inches (5.0 cm.) from the lower articular margin of the radius." This is a lesion of the sheath of the tendons of the extensores carpi radialis. This disease is due to a strain or excessive use of muscles. Direct trauma is the cause in 29% of cases, and indirect trauma in 70%. The lesion occurs in this manner; "the hand is firmly grasping some object, thus fixing the thumb and rendering the 3 dorsal muscles of the thumb tense and hard; the tendons of the extensores carpi radialis are now lying in a rigid tunnel. A sudden fierce movement of hyperextension or a series of hyperextension movements of the wrist lifts up the tendons of the extensores carpi radialis like a bowstring away from the radius and against the taut thumb muscles, as the bases of the

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metacarpals, where these tendons are inserted, move dorsally. This trauma produces tenosynovitis."

Treatment is rest in plaster of Paris, electrotherapy of all kinds, and counter irritants, ung. iodidi; the majority of cases clear up in 1 to 3 weeks.

J. A. STEWART DORRANCE

Metastasizing Goitre.

SHAW, R. C.: BRIT. J. SURG., 39: 25, 1951.

Aside from the well recognized forms of malignant disease of the thyroid gland, there is a rare group of atypical tumours showing metastatic propensities. It is no longer accepted that in this group only the metastases, usually in bone, are malignant, for careful examination will show a tumour in the gland even though it is slow growing and of negligible size compared to the metastases. One such type is the "latent cancer" of Correl, another the struma post-branchialis of Langhans and Getzowa. A third is the "Hurthle-cell tumour". A case report of this type is the basis for this paper. The pathogenesis is discussed.

Treatment advocated is resection of the primary thyroid tumour after biopsy of the obscure bone tumour shows it to be a case of metastasizing goitre. The nature of the source of the metastases may be obscure as it was in this case, for it looked very like a renal-cell carcinoma. The secondary lesion may be attached by radiotherapy once the primary has been resected.

It is suggested that the so-called very rare Hurthle-cell metastasizing tumour corresponds to the Langhans and Getzowa struma post branchialis. Some consider it to be of parathyroid origin. BURNS PLEWES

OBSTETRICS AND GYNÆCOLOGY

Gastric Aspiration as a Technique for the Prevention of Asphyxia in the Newborn Infant.

LITTLE, D. M., D'ANDREA, F. H. AND MASTRANGELO, A.: SURG., GYNEC. & OBST., 90: 363, 1951.

A syndrome of delayed respiratory distress may occur in the newborn infant, some minutes to hours after delivery and the initiation of apparently normal respiratory activity. It has been postulated that if an excessive amount of amniotic fluid were ingested at or prior to delivery it might be regurgitated and aspirated, thus accounting for the late onset of respiratory embarrassment. Gastric aspiration has been performed on all infants born by Cæsarean section as a prophylactic measure in order to prevent the development of this delayed form of respiratory distress. The use of this technique for a 12-month period coincided with fetal mortality rates approximately 50% lower than those obtaining for a previous 12-month control period.

ROSS MITCHELL

A Case of Hypersensitivity to Pethidine (Demerol) in a Woman in Labour.

BUTLER, E. B.: BRIT. M. J., 2: 715, 1951.

A case of cyanosis, rash, disappearance of pulse followed in five minutes by normal delivery of a fresh stillborn infant is recorded. This occurred in a woman aged 24, three hours and ten minutes after the intramuscular injection of 100 mgm. pethidine (demerol). Twenty minutes after the collapse a weak pulse could be felt and the blood pressure was 70/?. Her condition continued to improve and two hours later her blood pressure was 120/80 as on admission. Subsequently a test was taken after 50 mgm. pethidine (demerol) had been given intramuscularly. The maximum fall in blood pressure of 20 mm. occurred four hours after pethidine had been given. Even with normal dosage of a commonly used and usually safe drug, unexpected and serious reactions may occur. ROSS MITCHELL

INDUSTRIAL MEDICINE

Non-Sensitization of Nylon Thread.

JENNES, S. W.: INDUST. MED., 20: 272, 1951.

Since nylon came into use as a fabric in 1940, it has frequently been suspected as a cause of contact dermatitis. In this article reference is made to several investigations previously reported in the literature in each of which it had been concluded that the cause was not the undyed nylon. In several cases of suspected nylon sensitivity it was indicated that the sensitivity was due to the resin applied to the stocking as a finish; in another group of subjects patch testing revealed that the condition was due to a dye and not to the undyed fibre.

The author then presents details of a study recently carried out in the plant of Heminway and Bartlett, in Watertown, Conn., to determine the possibility of sensitization to undyed nylon. In this plant the major output is nylon thread prepared for various industrial purposes such as sewing spools, fishing lines, etc. At the time of study, the firm employed approximately 150 persons. Of these, approximately 100 had been employed and had been in intimate contact with nylon for nine years; the remaining 50 had been in contact with it for periods varying from three months to nine years. There had been no report of a dermatitis from the handling of nylon thread in any form.

Thirty subjects were chosen for this study. Of these, twenty-five were female employees selected at random, five of whom gave a past history of some allergic disease and five a positive allergic family history. The other five subjects were patients from the author's private practice who had contact eczema due to various etiological agents.

The thirty individuals were patch tested to nylon thread moistened in water and to nylon flake dissolved in alcohol. Details are given of the procedure. Patches were left on for 48 hours and examined. The subjects were questioned regarding pruritus at the end of 24 and 72 hours, and also at the end of seven days. There was no indication of a dermatitis on any of the tested sites and none of the individuals tested complained of itching. In the author's opinion sufficient evidence was obtained to prove that undyed nylon thread is non-sensitizing. MARGARET H. WILTON

Alcoholism in Industry.

THOMPSON, G. N.: INDUST. MED., 20: 273, 1951.

Placing workers in jobs for which they are unsuited, enforcing factors of stress to which we would not subject a mechanical contrivance, and expecting performance beyond the capacity of the emotionally handicapped person, are indicated in this article as factors contributing to industrial alcoholism. In the author's opinion, industrial alcoholism plays more havoc with the smooth operation of the industrial machine than any illness or emotional disturbance other than the common cold and perhaps dysmenorrhœa.

The causes of drinking, the nature of the alcoholic, and the mental disorders that result from the prolonged over-use of alcohol, are discussed. The author is particularly interested in the disorders of personality as causes of alcoholism and gives details regarding them. Alcoholism is a disease that affects the emotionally handicapped. That the alcoholic does not have a well-integrated personality is apparent. He is not receiving stimuli from the environment adequate to bring about the integration he needs. The studies of previous investigators have indicated that the alcoholic needs "a periodic escape" from his own personality characteristics; the author feels that rather than escape from these characteristics the alcoholic is attempting to ventilate them. Alcohol makes this expression possible.

The incidence of alcoholism among different occupational groups is of particular importance to industrial medicine. No one group seems to have more alcoholic patients than others, but a week-end retreat into alcoholism is almost the rule with many industrial workers.

Reference is made to psychotherapy as the obvious treatment for the personality disorder basic to alcoholism. The use of antabuse is also mentioned. In order to combat the increasing problem of industrial alcoholism, the author presents certain recommendations to industrial organizations. They include the following: (1) It is the duty of psychiatrists to assist industrial management to understand alcoholism as an illness. (2) The emotionally handicapped person who has alcoholism as a problem should be referred for psychiatric evaluation and treatment. . . The help of Alcoholics Anonymous should be sought wherever practicable. (3) Where adequate public agencies for the treatment of alcoholism do not exist, state or other public funds should be appropriated for the use of private treatment agencies, so that patients can be treated who would otherwise go without help. (4) It is recommended that insurance plans and sick benefits be extended to cover alcoholism and its treatment, in order that industrial employees may be treated for alcoholism without penalty of loss of time or wages because of their illnesses—*i.e.*, their drinking. (5) It is urged that wherever possible, state or Federal tax funds derived from the sale of alcoholic beverages should be used for the treatment and rehabilitation of alcoholic patients, as well as for further research into the causes and treatment of the disorder.

MARGARET H. WILTON

PÆDIATRICS

Hyaluronidase.

SCHWARTZMAN, J.: J. PEDIAT., 39: 491, 1951.

The literature is reviewed and methods of assay are described. The advantages in the use of hyaluronidase are: no detailed set up; no experienced personnel; the infusions may be given anywhere, home, hospital, or field hospital; it may be started without delay or preparation of the patient; the flow may be adjusted according to needs; the flow may be stopped or started at will with the needle left *in situ* as there is no concern over clots forming in the needle; there is no direct involvement of the vascular system, hence no danger of emboli or phlebitis; low incidence of patient sensitivity and toxicity; it increases clysis flow five- to fourteen-fold; when used with local anæsthesia the area and speed are increased by 40%; higher therapeutic levels of drugs may be maintained; the patient suffers less pain and inconvenience; and it facilitates fluid administration when veins are inaccessible. The contra-indications are: it should not be injected directly into areas of localized infection; when given in cases of sepsis, concurrent chemotherapy must be given; it should not be given to patients proven sensitive to it by routine pre-use intradermal skin testing; it should not be given in hypoproteinæmia until the total blood protein is at least 5.3 to 5.5%; and in cardiovascular disturbances extreme care must be used to prevent over-hydration. Complications are: pseudosensitive reactions with delayed onset; true sensitization; failure of absorption due to changes in biochemical levels secondary to infection; improper insertion of the needles between fascial planes; œdema when the tissues are saturated with fluid; and infections and local irritation.

The clysis needle is inserted into the subcutaneous tissues and 25 to 50 ml. of the infusion is allowed to run in, then 500 viscosity units of hyaluronidase in 10 ml. normal saline is injected into the tubing near the needle, this will permit increased flow for 24 to 48 hours when another 500 units may be injected.

J. A. STEWART DORRANCE

Treatment of Leukæmia in Childhood.

MICKLE, K. C. *et al.*: J. PEDIAT., 39: 442, 1951.

Twenty-two children with leukæmia were treated with aminopterin, amethopterin, and ACTH and/or cortisone. The antifolic acid drugs were given parenterally and orally. Aminopterin and amethopterin, folic acid antagonists, have some toxic side-reactions—ulcerative stomatitis, alopecia, pancytopenia, and hæmorrhage. When aminopterin is given in doses of 1.0 mgm. per day there is a reduction of the total white cell count in the peripheral blood, in some cases to 1,000 cells per c.mm. The immature cells were reduced by the second day, blast cells and granulocytes disappeared, and small lymphocytes appeared. Thrombocytes increased in number and returned to normal levels until the onset of an exacerbation. Bone marrow studies were of no great benefit. During intensive therapy the red blood cells and hæmoglobin fell to very low levels and in some cases necessitated transfusion of whole blood. Antifolic acid treatment has little value after the end of the first remission. Aminopterin relieves pain due to leukæmic infiltration of the marrow and is the most effective agent in reducing the size of enlarged lymph nodes, liver and spleen, thereby relieving the distressing symptoms of abdominal and mediastinal pressure. The effect of ACTH and cortisone is less effective than that of antifolic acid agents.

J. A. STEWART DORRANCE

The Molecular Structure of Skin, Hair, and Related Tissues.

ASTBURY, W. T.: BRIT. J. DERMAT., 62: 1, 1950.

This lengthy article by Professor Astbury of the Department of Biomolecular Sstructure at the University of Leeds should be read by those interested, in conjunction with the brief article on Electron Microscope Study of Epidermal Fibres abstracted from *Science*.

Before the advent of the electron microscope, it is stated that it was proved by x-ray diffraction analysis plus high polymer chemistry that natural fibres are molecular yarns constructed of chain-molecules lying along the length of the fibre, and this is the essence of modern textile science. Thus the material fabric of life is largely woven from chain-molecules, vital activity being principally an expression of the properties of proteins, polysaccharides and nucleic acids in collaboration with smaller accessory molecules. Whether protein structures are visibly fibrous or not they are all fibrous in the final sense, always being systems of polypeptide chains, alone or in combination with polysaccarides or nucleic acids. Together with their side-chains, the main-chain is capable of almost free rotation *about* the chemical bonds, yet keeping the characteristic inter-atomic distances and bond angles. Changes of form in long chain-molecules are the chief basis of biological movement and activity. Keratin molecules of hair give two x-ray diagrams (not radiographs but diffraction patterns) according to whether they are stretched or unstretched, thus may be considered as minute springs. Curls and waves in hair are on an enormously longer scale and there is no relation between them and the α and β keratin of the "temporary" and "permanent" set in the "curling paper wave" and the "permanent" wave respectively. The natural curves and waves in hair give the same kind of α-diagram, being the result of rhythmic movements of the follicle during growth. The elastic properties and x-ray diagrams of mammalian hairs hold good for horn, nails, hooves, hedgehog spines, porcupine quills, whalebone, etc., but not for avian and reptilian keratin. They are on the same molecular level, differing in degree but not in kind. Essentially the same x-ray diagrams are furnished by the fibrous proteins of the epidermis, myosin, paramyosin and tropomyosin, fibrinogen and fibrin and bacterial flagella. This group has therefore been called the keratin-myosin-epidermis-fibrinoge n (k-e-m-f) group. Myosin is an analogue of keratin, except that it is much more labile.

Non-mammalian keratin and its analogue have not the same x-ray type of structure, examples being feathers,

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birds' beaks and claws, tortoise-shell, snakes' scales, lizards' claws, etc. X-ray classification of the keratinous-fibrous proteins is a study in the molecular phylogeny underlying the large-scale phylogeny of classical biology. The diffraction diagrams show however that the non-mammalian keratin structure is after all a disguised β-type analogous to *stretched* hair, thus is a β-sub-group of the k-e-m-f group.

From the x-ray viewpoint epidermis can not only produce α-type keratin, the analogue of α-myosin in muscle, but also keratin of the feather type, and in the muscle complex a hypothetical counterpart of feather keratin. This is the new muscle protein, actin, of Szent-Györgyi and his school which appears to show that the seat of muscle contraction is a combination of myosin and actin called actomyosin. Whether the myosin is contracted or not depends upon its state of interaction with actin, which in turn depends upon a preferential interaction between myosin and adenosine tri-phosphate.

Almost all the remaining fibrous proteins are shown by x-rays to belong to what the writer calls the collagen group, because they give a type of diagram like that of collagen fibres. It includes the white connective-tissue fibres, tendons, cartilage, cornea and other parts of the eye, scales and fins of fishes, ichthyocol of swim-bladders, byssus threads of bivalves, cuticles of annelid worms, jelly-fish, ejectable filaments of sea-cucumber, etc. These have a molecular plan giving an x-ray diagram quite different from that of the k-e-m-f group. Broadly speaking the whole skin exemplifies both great families of fibrous proteins, the k-e-m-f group of the epidermis and the collagen group of the epidermis. No change has been brought about in the collagen diagram like that produced by stretching members of the k-e-m-f group; the collagen chain-molecules are effectively inextensible, but they have the important property of thermal contraction. Elastin is distinguished from collagen by its rubber-like elacticity, and from the x-ray diagram is apparently not a member of the collagen group proper. By means of the electron microscope a great advance in the knowledge of collagen has been made. It has revealed the important transverse banded structure of the collagen-fibre, and this in turn has been studied by the x-ray diffraction, although a satisfactory interpretation has not been reached. Further study with these agencies is necessary before the relation of skin behaviour to its fine structure, and the elucidation of the problems of biogenesis, as the generation of the fibrils in the cuticle of the earthworm, which forms the basis of the present study, can be discussed with confidence.

D. E. H. CLEVELAND

FORTHCOMING MEETINGS

CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS, First Mid-Winter Annual Meeting, Winnipeg, Man., January 16 to 18, 1952.

AMERICAN COLLEGE OF SURGEONS, Sectional Meeting, Chateau Frontenac, Quebec City, Quebec. (In honour of the Centenary Year of Laval University), February 18 and 19, 1952.

CANADIAN MEDICAL ASSOCIATION, Annual Meeting, Banff, Alta., June 9 to 13, 1952.

UNITED STATES

AMERICAN CONGRESS ON OBSTETRICS AND GYNÆCOLOGY, Fifth Congress, Netherland Plaza Hotel, Cincinnati, Ohio, March 31 to April 4, 1952.

AMERICAN GOITRE ASSOCIATION, Annual Meeting, Saint Louis, Missouri, May 1 to 3, 1952.

AMERICAN ASSOCIATION FOR THORACIC SURGERY, Dallas, Texas, May 8 to 10, 1952.

NATIONAL TUBERCULOSIS ASSOCIATION, Annual Meeting, Statler Hotel, Boston, Mass., May 26 to 29, 1952.

AMERICAN MEDICAL ASSOCIATION, Annual Session, Chicago, Ill., June 9 to 13, 1952.

AMERICAN UROLOGICAL ASSOCIATION, Annual Meeting, Chalfonte-Haddon Hall, Atlantic City, N.J., June 23 to 26, 1952.

OTHER COUNTRIES

PAN-AMERICAN CONGRESS OF OPHTHALMOLOGY, Fourth Congress, Mexico City, Mexico, January 6 to 12, 1952.

BRITISH CONGRESS OF OBSTETRICS AND GYNÆCOLOGY, 13th Congress, The Hospital for Women, Coventry Place, Leeds, Yorkshire, England.

COMMONWEALTH AND EMPIRE HEALTH AND TUBERCULOSIS CONFERENCE, Third Conference, Central Hall, London, England, July 8 to 13, 1952.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, London, England, July 14 to 19, 1952.

INTERNATIONAL CONGRESS OF DERMATOLOGY, Fourth Congress, London, England, July 21 to 26, 1952 (Dr. G. B. Mitchell-Higgs, St. Johns Hospital, Lisle Street, Leicester Square, London, W.C.2).

NEWS ITEMS

NEWS OF THE MEDICAL SERVICES

Further Defence Co-operation

Speaking at the annual meeting of the Defence Medical Association in November, Defence Minister Brooke Claxton reviewed the general situation, relating this to Canada's participation in Korea and Europe. He said:

"The expansion during twelve months of the armed forces from 54,000 to 86,000, 75%, involved a corresponding expansion in officers and increased substantially the requirements for medical officers. Medical schools in the universities were co-operating, particularly through the university plan, under which medical students could be taken on strength at the beginning of their final year, receiving full pay and allowances until they qualified.

"Wartime experience has shown the advantage of having the closest working arrangements with the medical and dental professions. To extend this today I set up the Defence Medical and Dental Services Advisory Board. On this Board are the heads of the medical services of the Navy, Army and Air Force and of the dental service, and representatives of the Departments of Veterans' Affairs, Health and Welfare and Labour, as well as of the Canadian Medical Association, the Canadian Dental Association and the Canadian Hospital Association.

"To make this effective, an outstanding civilian doctor has been appointed as Chairman. He is Dr. Emmet McCusker, M.P., Parliamentary Assistant to the Minister of National Health and Welfare, who has served as a brigadier and Deputy Director General of Medical Services.

"While a great deal had been done to promote the utmost economy in the use of professional medical services, I have approved DMDSAB setting up a committee to look into the question of their further integration particularly from the professional point of view.

"The committee consists of Dr. G. E. Hall, President of the University of Western Ontario, London; Dr. J. A. McFarlane, Dean of the Faculty of Medicine, University of Toronto; Dr. W. C. Mackenzie, Professor of Surgery, University of Alberta and Dr. Mathieu Samson of Quebec.

"It will be meeting at Ottawa shortly and will in the course of its work inspect a number of defence establishments and consult with senior service personnel, as well as members of the medical profession who had had outstanding service experience."

Surgeon Commodore Archie McCallum, O.B.E., V.R.D., C.D., M.D., was recently promoted in the Order of St. John of Jerusalem from Brother Officer to the rank of Commander Brother and was invested with the Order by His Excellency The Governor General at Government House in Ottawa on November 12, 1951.

Colonel K. A. Hunter, O.B.E., C.D., M.D., Deputy Director General of Medical Services, Army Headquarters, Ottawa, formerly Command Medical Officer, Central Command, Oakville, Ont., was recently appointed to the Order of St. John of Jerusalem in the grade of serving brother. Colonel Hunter was invested with the Order by His Excellency The Governor General at Government House, Ottawa, on November 12, 1951.

The annual Conference of the Command and Area Medical Officers of the Army was held at Army Headquarters, Ottawa, on November 7 and 8, 1951, under the chairmanship of Brigadier W. L. Coke, O.B.E., C.D., R.C.A.M.C., Director General of Medical Services (Army).

Following the Conference, on November 9 and 10, the Officers attended the annual meeting of the Defence Medical Association which took place at the Chateau Laurier, Ottawa, under the presidency of Group Captain A. D. Kelly of Toronto, Ontario.

The following medical officers were recently promoted to the rank of Colonel: Colonel E. E. Tieman, O.B.E., C.D., R.C.A.M.C., Command Medical Officer, Eastern Command, Halifax, N.S. Colonel R. J. Nodwell, C.D., R.C.A.M.C., Canadian Army Medical Liaison Officer, Washington, D.C. Colonel G. L. M. Smith, O.B.E., C.D., R.C.A.M.C., Commandant, The R.C.A.M.C. School, Camp Borden, Ontario.

Major F. C. Pace, C.D., R.C.A.M.C., Officer Commanding, ABCD Wing, The R.C.A.M.C. School, Camp Borden, Ontario, was recently appointed to the rank of Lieutenant-Colonel.

In accordance with the rotation policy for personnel serving in the Far East Major E. H. Anderson and Captain E. Karpetz have returned to Canada after serving in Japan and Korea for one year and Captain C. J. Thiel, Major J. S. Hitman and Captain R. K. Schryer have been posted to the Eastern Theatre.

No. 1 Fighter Wing, R.C.A.F., North Luffenham, Rutland, England, the formation of which was recently announced by the Minister of National Defence, has the following Medical Officers and Nursing Sisters on staff: Squadron Leader J. McElroy, Medical Officer; Squadron Leader W. W. Laughland, Medical Officer; Flight Lieutenant W. F. Jacobs, Medical Officer; Flight Lieutenant V. M. Bransager, Nursing Sister; Pilot Officer M. F. Cavanagh, Nursing Sister.

Defence Research Board has instituted a flight feeding study. The problems of pre-, in- and post-flight feeding will be investigated by this group. The R.C.A.F. is represented by Squadron Leader A. M. Beach, Senior Medical Officer, R.C.A.F. Station, Lachine, and Flying Officer Barbara Ross, Messing Officer, R.C.A.F. Station, Trenton.

A new program for Nursing Sisters has recently been inaugurated. This course is of one month's duration and will include two weeks at the Indoctrination Course, London, Ont., and two weeks at the Institute of Aviation Medicine, Toronto, studying medical service procedure. The first course started in London, December 3, 1951.

« Important Income Tax Information »

Many physicians who practise in partnership have been affected by rulings of the Income Tax Appeal Board, which had the effect of requiring them to claim deductions for the legitimate expenses of practice from the partnership income rather than in their personal income tax returns. The application of this ruling to the taxation years 1949 and 1950 has resulted in the disallowance of practice expenses claimed in personal returns for those years and in assessment for additional tax.

A recent directive from the Department of National Revenue to District Income Tax Offices cancels this ruling and taxpayers who are partners may continue to claim as deductions in their personal returns the allowable expenses of earning their income. The situation therefore reverts to that which applied before the ruling of the Appeal Board in the case of "Mr. I".

Doctors who have paid additional tax for 1949 and 1950 as a consequence of the disallowance of expenses charged in their personal income tax returns, *should make written application for refund without delay.*

Section 52(i) of the Income Tax Act, quoted hereunder, applies;

"The Minister may, upon mailing the notice of assessment, refund, without application therefor, any overpayment made on account of the tax and he shall make such a refund after mailing the notice of assessment if application in writing is made therefor by the taxpayer within 12 months from the day the overpayment was made or the day on which notice of assessment was sent."

If you have made overpayment under these circumstances and have not made an appeal or have not already made application for adjustment, you are strongly advised to apply in writing to your District Income Tax Office for a refund before the expiry of twelve months from the overpayment.

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ALBERTA

Dr. L. A. Rook a recent arrival from England has joined the Medical Arts Clinic in Medicine Hat. Dr. Rook holds the degrees of M.A., M.B., B.Ch., M.R.C.S., D.O.M.S.

Dr. J. A. McNally has joined the staff of the Drs. Roy, Schmaltz, Rice Clinic in Lethbridge. During the war Dr. McNally served overseas with the R.C.A.M.C.

Dr. William Boyd, Professor of Pathology at the University of British Columbia Medical School, was the speaker at the annual banquet of the Edmonton Academy of Medicine.

Dr. Colin A. Ross, a graduate of the University of Alberta, has returned to Edmonton where he is confining his practice to thoracic surgery. Dr. Ross took his postgraduate training in thoracic surgery under Mr. George Mason, F.R.C.S. in Newcastle-upon-Tyne. A period of two and a half years was spent followed by a tour of the Scandinavian thoracic clinics.

Dr. Morley Tuttle of Calgary and Dr. G. S. Gray of Lethbridge have been appointed associate editors to the *Alberta Medical Bulletin*.

The Cancer Diagnostic Clinic in Edmonton is being reorganized during the move to the new quarters on the University Hospital grounds. The Act pertaining to cancer treatment has been revised and a copy is in the hands of all the practitioners of the Province.

W. CARLETON WHITESIDE

BRITISH COLUMBIA

The idea of a rehabilitation centre for drug and alcoholic addicts has for some time been the subject of discussion in British Columbia; and the Attorney-General, Hon. Gordon Wismer, has been particularly interested in the project. He has, we understand from press reports, been in communication with Federal authorities in the person of the Hon. Paul Martin, Federal Minister of Health, on this subject.

A preliminary survey, by trained psychologists, will probably be the first step to be taken, and these gentlemen will study the results of work being done in various centres, such as Lexington, Kentucky. Following this survey, the local possibilities will be explored.

The annual report of the British Columbia Cancer Institute made at its annual meeting, makes very interesting reading. There has been a steady growth in the number of patients seen, and in the number of positive diagnoses of cancer. This is being discovered earlier, as the public appreciates the work of the Institute, and as doctors make more and more use of its facilities. One seems to notice a greater readiness on the part of patients to go there, and a lessening of the dread that the mere mention of the "Cancer Institute" used to engender. That this is so, is no doubt mainly due to the kindly, yet matter-of-fact, attitude of the Clinic—and to some extent, also, we think, to their excellent publicity and educational programs.

The new buildings of the Institute are nearly completed. The Medical Director, Dr. A. M. Evans, states that in his opinion, these will prove adequate for a long time to come. He states, too, that plans are under way for installation of one of the new Cobalt bombs for radiotherapy. This, we are told, will be the sixth such bomb installed in Canada.

Dr. G. F. Strong was elected as the new President of the Institute, and we note the name of Dr. William Boyd, Professor of Pathology at the U.B.C. Medical School, in the list of Directors.

The death of Dr. E. H. Saunders, of Vancouver, marks the passing of one of British Columbia's pioneers in the specialty of eye, ear, nose and throat diseases. He came here in 1909, when there were not more than one or two specialists in this line, and was actively practising till within a very short time of his death at the age of 81. He was an extremely skilful man at his work, and had attained a position of authority in the subject.

Dr. Saunders graduated from McGill in 1895. Shortly before his death, he had been awarded a Life Membership in the Vancouver Medical Association. This only faintly hints at the high regard in which his fellows held him. Quite apart from his professional attainments, he was a man whom it was an honour to know—a man of the highest integrity, a man without an enemy, but with a myriad of friends.

Plans to establish a sick mariners' clinic in Victoria are, we understand, receiving very serious consideration. It would be situated, probably, in the Ogden Point area, where the Canadian Immigration buildings now are.

The chief medical officer for the Station, Dr. R. B. Jenkins, and his next in command, Dr. G. L. Sparks, would, it is presumed, be in charge of the Clinic.

The appointment of Dr. Elinor Black, as professor of obstetrics and gynæcology at the University of Manitoba, and chairman of the department, is of great interest. This is, we believe, the first time that this position has been filled by a woman in a Canadian medical school, and we must all congratulate Dr. Black most sincerely—as it is a most important position, and only sheer ability could win it.

Dr. Black's immediate family includes Miss Charlotte Black, Director of the School of Home Economics at the University of British Columbia, and Dr. Donald M. Black, who practises medicine at Kelowna. Another sister, Miss Marjorie Black, is on the staff of the Nurses' Training School of the Vancouver General Hospital.

The special Committee of the B.C. Legislature appointed to study the workings of the B.C. Hospital Scheme, is now engaged, we learn, in completing its report, which will be presented at the forthcoming session of the Legislature. Till it is presented, of course, there is no knowing what recommendations will be made. In the meantime, the Minister of Health, the Hon. A. D. Turnbull, has been making every effort in his power to make the working of the Act fall more lightly on those who are in arrears with their dues, and has made some very important concessions in this matter. These concessions have produced some result but not as much as was hoped, and we understand that they will not be continued indefinitely.

A moderate sized epidemic of scarlet fever is at present present in Vancouver. The disease is of a notably mild type, and is apparently thoroughly under control.

J. H. MACDERMOT

MANITOBA

A memorial service was held in Norwood United Church on November 18 for Dr. Merle Patterson, a missionary of the United Church of Canada, who was killed on October 27 in a motor car accident in India. She graduated from Manitoba University in 1942.

The Manitoba Medico-Legal Society was formed on November 6 at a meeting held in the Manitoba Club. A planning committee was formed consisting of Drs. C. E. Corrigan, A. M. Goodwin, M. T. MacFarland, Mr. B. V. Richardson and Mr. John L. Carpenter. The society will meet each month and the first full meeting is being held in January, 1952.

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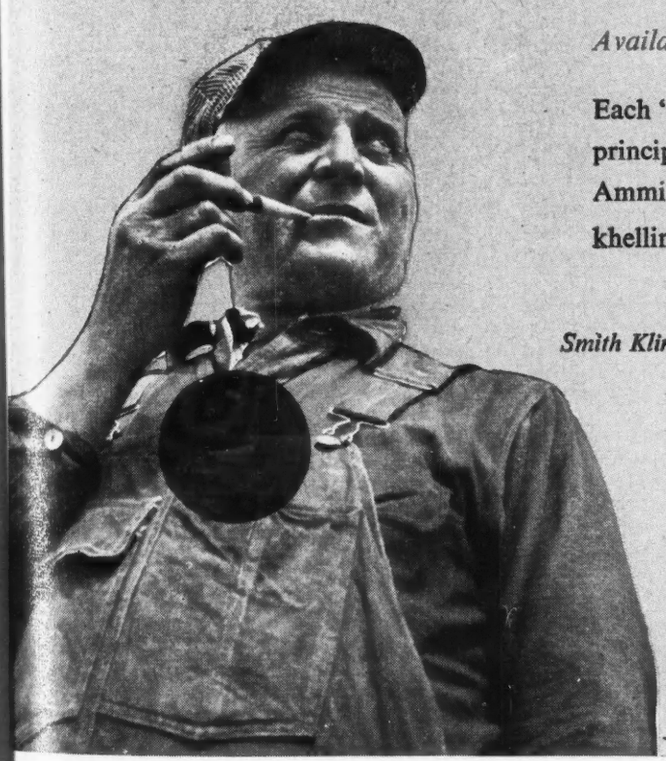

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Sir Edward Mellanby, G.B.E., K.C.B., Medical Research Council, London, England, delivered a Tisdall Memorial Lecture on "Physiological Aspects of Nutrition" under the joint auspices of the College of Physicians and Surgeons of Manitoba and the Winnipeg Medical Society in the Medical College on November 14. It was enthusiastically received.

Dr. James Hendry of Aberdeen has recently joined the staff of the Health Department of Winnipeg.

The *Manitoba Gazette*, November 3, reports that Dr. J. D. Adamson is a member and Chairman of the Advisory Commission under the Manitoba Health Services Act, effective Oct. 1, 1951. He replaces Judge George of Morden who has retired after having served two periods of three years.

Dr. Elinor F. E. Black has been appointed chairman of the Department of Obstetrics and Gynæcology, Faculty of Medicine, University of Manitoba and has been raised from assistant Professor to Professor. She succeeds Dr. F. G. McGuinness who retired on December 1.

Dr. Brian D. Best of the same department, has been promoted from assistant professor to Professor.

ROSS MITCHELL

NEW BRUNSWICK

Viscount Alexander presented Dr. G. B. Peat of Saint John with Scouting's Silver Acorn at an investiture at Government House, Ottawa, early in November. Dr. Peat has completed thirty years' service in scouting in New Brunswick and is now President of the N.B. Boy Scouts Association.

Dr. T. E. Lunney read a paper on "Pain" at the monthly clinical staff meeting of Lancaster D.V.A. Hospital in November.

Dr. Christopher J. Duncan, gynæcologist of the Free Hospital for Women, Brookline, Mass., addressed the Saint John Medical Society on the subject, "Female Hygiene", at the regular November meeting. This visit was arranged while Dr. Duncan was in the Maritimes as a special speaker at Dalhousie University.

Dr. W. D. Stevenson, neuro-surgeon of Halifax, N.S., presented addresses on "Treatment of Head Injuries" at Moncton, Bathurst and Fredericton during the latter half of November. He was accompanied on this tour by Dr. Whitehead, secretary of the N.B. Medical Society.

The Medical Council of New Brunswick at its annual meeting in November elected Dr. V. A. Snow of Hampton, president for 1952. Dr. J. M. Barry was reappointed as Registrar.

Dr. Jean F. Webb of Saint John, who has been head of nutrition services for the N.B. Health Department and has lately completed courses at Harvard University School of Public Health, has been appointed as pædiatric consultant on the staff of the Child and Maternal Health Division of the Federal Health Department at Ottawa.

Dr. F. W. Stevenson of Saint John has completed a successful recovery following gastric surgery and is enjoying his convalescence.

A. STANLEY KIRKLAND

NOVA SCOTIA

The Refresher Course of Dalhousie Medical School held its Silver Jubilee the first week in November and attracted the largest registration it has had outside of the war years. Two hundred and thirty-five doctors from the four Maritime provinces registered for the mixed and concentrated program which ran the whole range of medicine, surgery and their specialties. Attending as guest teachers were Dr. W. E. Gallie, Toronto; Dr. Richard Chute, Associate Urologist of the Massachusetts General Hospital; Dr. Charles S. Davidson, of the Department of Medicine of the Boston City Hospital; Dr. E. C. Hamblen, Professor of Endocrinology and Gynæcology at Duke University; and Dr. Alan Ross, Assistant Professor in Pædiatrics at McGill. Supported by the staff of the Medical School and with motion pictures to fill in the early morning and late evening hours the program, designed particularly for general practitioners, ranged from anterior poliomyelitis to fractures of the spine, from urological congenital anomalies to a symposium on "Headaches".

The third annual John Stewart Memorial Lecture presented by Dr. Gallie on "Teaching and Research in Surgery" was an address profound in its study of the problems of advanced medical education and the medical student. Clinical presentations were held at the Victoria General Hospital and at Camp Hill Hospital and a feature of the meeting was a marked increase in the use of the round table, conducted on a question and answer basis, to stimulate informal discussion.

Dr. H. Leslie Stewart, Halifax, has been appointed to the surgical staff of the Victoria General Hospital. Dr. D. J. Tonning, Dr. R. M. MacDonald and Dr. L. C. Steeves have been promoted from Assistant to Associate positions on the hospital staff.

The need for physical and occupational therapists in Nova Scotia has been stressed by the local Committee of Trauma of the American College of Surgeons, and also by Dr. W. D. Stevenson of the Department of Neurosurgery of the Victoria General Hospital in addressing the Nova Scotia branch of Occupational Therapy. There seems little doubt that looked at from the most mercenary point of view the cost of an adequate staff of physiotherapists in the province could be paid many times over by the reduction thereby attained in the disability periods and permanent disability among industrial workers.

Dr. Helen Holden Quinlan, of the staff of the Nova Scotia Sanatorium, has been awarded a Fellowship in the American College of Chest Physicians.

The third Maritime Institute for Hospital Administrators, Trustees and Department Heads met during the last week in November at the Victoria General Hospital. Coming up for discussion during the meeting were fire prevention in hospitals, medical records, space, equipment and personnel, small hospital x-ray department, nursing staff personnel problems, precautionary techniques in general hospitals and civil defence. Sponsored by the Maritime Hospital Association this meeting of the Institute was under the direction of Sister Catherine Gerard, Superintendent of the Halifax Infirmary.

Dr. S. W. Williamson of Yarmouth was guest of honour at the annual banquet of the Dalhousie Medical Students' Society. In paying tribute to the general practitioner the students could have chosen no more worthy representative. A graduate of the old Halifax Medical School in 1896, Dr. Williamson at 83 is still carrying on his active general practice. Two years ago, he told his hosts, on the advice of his own physician following an illness, he reduced his sixteen hour working day some-

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what and does less night work than before. This he has found to have worked out very advantageously because he now has his evenings relatively free to devote to his medical journals, and for the first time in his years of practice he has been able to keep abreast of modern medicine in all its phases. This has given him a greater pleasure than any of his many endeavours in the fifty-five years of his practice. Dr. Williamson had no envy for the modern medical student because he hopes to march along with him for some time yet; he did regret that the student of today lacks the intimate knowledge of practice half a century ago, and hence has difficulty in developing a true appreciation for the advances medicine has made and the great power of the healing agents he now possesses. Dr. Williamson's career has been a guiding light for his younger confrères as well as for the student of Dalhousie. ARTHUR L. MURPHY

ONTARIO

The new Osler Hall of the Toronto Academy of Medicine was officially opened on November 16 by Dr. W. E. Gallie. Built at a cost of $200,000, the new hall, second Academy building to bear this name has an auditorium capable of seating 325 and a basement stack room which can hold 50,000 volumes and periodicals. At the conclusion of his address, in which he described the rôle of Sir William Osler, who helped found the Academy forty years ago Dr. Gallie presented the Academy with two medical volumes, "Les Annales de L'Hotel-Dieu de Quebec, 1636-1716" and "The Works of Ambroise Paré 1634". Only 30 copies of this book exist; this is the only one in Canada.

Miss Edna M. Poole, chief librarian of the Academy, who will retire this year after 29 years in this work was presented with a radio. Dr. Gordon Cameron, chairman of the building committee was given a silver cigarette case as a token of appreciation for his watchful care over the new building.

The first president of the Academy was Dr. J. F. W. Ross whose son, Dr. James Ross, is the president now. The new auditorium is built on the plan of a theatre, the floor is sloping and the seats are comfortable. The seats and walls are a light green while the floor and the stage curtains are rust coloured. Members and their wives came in throngs to the official opening.

Dr. Richard Maddock, Wayne University, Detroit, addressed the Essex County Medical Society on "The Male Eunuchoid". He described the various types and emphasized the necessity of carrying out adequate laboratory studies before starting treatment. In cases of hypogonadotropic eunuchoidism the recommended treatment is 5,000 units chorionic gonadotropin three times a week for three months followed by a rest of three months. In instances of hypergonadropic enunuchoidism replacement therapy is the treatment of choice. Testosterone therapy is contraindicated in cryptorchidism.

Essex County Medical Society is organizing an emergency roster to maintain and improve medical service at all times, that is a twenty-four hour service for 365 days a year.

Dean MacFarlane of Toronto has been elected president of the Association of Canadian Medical Colleges.

Dr. Elizabeth Chant Robertson of the Department of Pædiatrics and Hospital for Sick Children has published a book called "Nutrition for Today".

A grant of $4,000 has been received by the University of Toronto from the Kellogg Foundation to finance a pilot study in decentralized postgraduate medical education. Teachers will go out from the university to conduct special rounds in the hospitals at Fort William-Port Arthur, Welland and Kirkland Lake. Six such sessions will be held in each of these centre during the coming year.

The Samuel Godfrey Scholarship was awarded to Miss Sharon Nabeta and the Medical Alumni Association Scholarship to Kenneth McCuaig, both of the first pre-medical year, Toronto. LILLIAN A. CHASE

QUEBEC

The Quebec Association of Pathologists has drawn up certain resolutions on the subject of a central diagnostic service in the Province. It is pointed out that the systematic histological examination of all surgically removed specimens is indispensable in maintaining high standards of medical practice; that hospitals must meet the requirements of such examinations for approval for internship; that there are too few competent pathologists to provide on the spot services to all the hospitals in the province; that such a service is sought by various bodies and hospitals.

In view of this, it was resolved that a Histologic Diagnostic Service of the Quebec Association of Pathologists should be set up with various regulations as to its membership. The executive committee of the Quebec Association of Pathologists would assume the administration of this service and was empowered to add members or create a special committee. The Diagnostic Service Committee would have the authority to bill and collect all examination fees, which would be distributed twice yearly on a pro rata basis to the respective participating pathologists. Specimens sent directly to a pathologist from a physician would be charged for by the pathologist himself. For institutions sending their material to participating pathologists, the minimum fee per specimen would be $6.00. Of this amount, $5.00 would cover the fee of the consulting pathologist and $1.00 the expense of histological technique.

The Anæsthetists of the Province of Quebec were well represented at the Washington meeting of the American Society of Anæsthesiologists which was held from November 5 to 8. There is a large membership in this Society from the Province. Dr. Wesley Bourne gave one of the refresher courses.

The International Congress of Anæsthetists held in London and Paris during September was an extremely successful gathering. Representatives from many countries were present and the quality of the papers was excellent. Six members from the Province of Quebec attended, two of whom gave papers at the Paris meetings. Dr. Harold Griffiths was chairman of one of the sessions held in London.

GENERAL

A former director of nutrition services for New Brunswick, Dr. Jean F. Webb, Saint John, has been appointed by the Civil Service Commission as a pædiatric consultant on the staff of the child and maternal health division of the federal health department.

Dr. Webb will assist the director of the child and maternal health division, Dr. Ernest Couture, in planning new developments to improve the health of mothers and children and to reduce the infant mortality rate. She will also assist provincial authorities in planning and organizing specific phases of their child and maternal health programs.

Dr. Webb was born in Saint John, N.B., and holds degrees in science from Acadia University, in medicine from McGill and in public health from Toronto.

A Sectional Meeting of the American College of Surgeons will be held in Quebec City on February 18 and 19, 1952, at the Chateau Frontenac. This will be in honour of the centenary year of Laval University.

The program will contain papers in French and English and outstanding surgeons from all over America will participate in the scientific program.

The Canadian Society of Laboratory Technologists is holding its 16th Annual Convention in Niagara Falls, Ont., during the month of May, 1952. Headquarters for the Convention will be the conveniently located General Brock Hotel, overlooking the beautiful Oakes Garden Theatre and the majestic cataract. It cannot be stressed too strongly that reservations for the Convention MUST be in the hands of Miss Dorothy Deitch, c/o the Laboratory, Greater Niagara General Hospital, Niagara Falls, Ont. NOT LATER THAN April 20.

Miss N. D. Fidler, director of the Metropolitan School of Nursing, Windsor, Ont., has been appointed to the Dominion Council of Health. The Dominion Council of Health is composed of the deputy ministers of health or the chief medical officers of the 10 provinces and five other persons representing labour, agriculture, medical research, English-speaking women and French-speaking women. In recent years the representative of English-speaking women has been someone trained in nursing. The Council meets in Ottawa twice a year to discuss current health problems and to work out common approaches to them. Miss Fidler, whose appointment is for a three-year term, succeeds Miss Elizabeth Smellie, Ottawa.

Scholarships valued at $6,000 for postgraduate study in physical education, recreation or physical medicine are to be awarded this year by the National Council on Physical Fitness. Set up three years ago to help overcome the scarcity of professional personnel with advanced training in physical education and recreation, the scholarships are for postgraduate study only and are restricted to Canadians who have had at least three years' full-time experience in physical education or recreation in Canada, including at least one year's experience since obtaining an under-graduate degree. The total value of the scholarships this year has been increased from $4,000 to $6,000. No award may be made for more than $1,200 or for less than $300. Deadline for applications is January 15, 1952.

Application forms are obtainable from provincial government fitness or recreation offices or from the National Council's office in the Department of National Health and Welfare, Ottawa.

The American Goitre Association again offers the Van Meter Prize Award of three hundred dollars and two honourable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Saint Louis, Missouri, May 1, 2 and 3, 1952, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy in duplicate sent to the Corresponding Secretary, Dr. George S. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, not later than March 1, 1952.

In accordance with the decision of the International Committee of Radiology which met in London in July, 1950, the 7th International Congress of Radiology will take place in Copenhagen in 1953. The dates of the Congress will be July 19 to 25.

Radiologists from throughout the world will be welcome at the Congress. All national radiological societies are being asked to supply a list of their members, and full details about registration for the Congress will be sent to all radiologists individually as soon as they are available. Correspondence should be addressed to the Congress Office at 10 Oster Voldgade, Copenhagen K.

It was with a great deal of pleasure that the Alberta Society of X-Ray Technicians learned from their delegates to the Dominion Convention, held in Winnipeg in September, that the next annual convention will be held in Calgary. Intermingled with the pleasure, was the realization that this would entail an enormous amount of effort to attain the high standard of the preceding conventions, and with this thought in mind, the various committees are already hard at work with arrangements for an interesting and instructive program.

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NOTICE.—Applications for Junior and Senior Internships. The Ottawa Civic Hospital is now accepting applications for a two year internship to prepare physicians for general practice. The first year to consist of a Junior Rotating service and the second year to consist of a Senior Rotating service made up of 3 months' Medicine, 3 months' General Surgery, 3 months' Obstetrics and 3 months' Pædiatrics. Applications for Junior and straight Senior Internships are also accepted. Apply to Secretary, Intern and Post Graduate Education Committee, Ottawa Civic Hospital, Ottawa, Canada.

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Continued on Page 36